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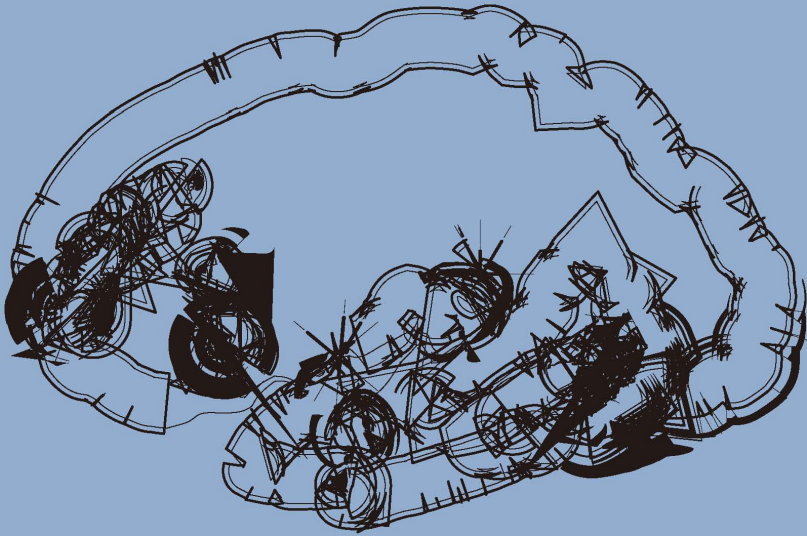
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The language networks of the brain



Huadong Xiang

DONDERS

series

The language networks of the brain

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Contents

1 Introduction	3
2 Topographical functional connectivity pattern in the perisylvian Language Network	11
3 L2-proficiency-dependent laterality shift in structural connectivity of brain language pathways	45
4 The structural connectivity underpinning language aptitude, working memory and IQ in the perisylvian language network	73
5 Genetic modulation of Broca's and Wernicke's area as structural hubs in the large-scale brain networks	91
6 Summary and discussion	105
References	115
Appendix	131
Supplementary Material for Chapter 3	133
Samenvatting	135
中文概述	141
Acknowledgements	145
CurriculumVitae	151
List of publications	152
Donders Graduate School for Cognitive Neuroscience Series	153

Chapter 1

Introduction

Welcome to my thesis! But wait..., why are you here? I mean, have you ever wondered why you opened this thesis? Maybe you are one of my family members or supervisors; maybe you are a friend who knows me well, or a bit; or maybe you are a reading committee member who has never heard of me. You want to, or have to read this thesis because you are really proud of or interested in its content, or you feel it is nice to produce some questions during my defence practice, or you just take it as your duty. In either way, you opened it because you and I are somehow connected, through love, friendship, responsibility or other people in this world. Our whole world is organized with connections and forms into networks, so does the human brain function for language.

In recent decades, the developments of non-invasive neuroimaging techniques have given rise to a boom of research in cognitive neuroscience. One of the most important neuroimaging techniques is fMRI (functional magnetic resonance imaging), which has often been used to localize specific functions to certain brain regions. However, recent studies have shown that human language processing employs brain networks involving multiple areas (Price 2010; Hagoort 2005a). It is thus a more precise and comprehensive way to study brain language function at the level of networks rather than considering isolated regions. And that is the way we approached the language system in this thesis. This thesis contains studies that investigate the language function at the neuronal network level and the connectivity among language areas in the brain.

In the following paragraphs of this introduction, I will briefly introduce the concepts and techniques used in this thesis.

The perisylvian language network

The study of language networks started from the most classical one, i.e., the so called 'perisylvian language network'. Early anatomical models of the perisylvian language network are mainly based on Broca's and Wernicke's classical clinical observations on aphasic patients. It consisted of Brodmann area (BA) 44, 45 in the inferior frontal lobe (Broca's area), the superior posterior temporal lobe (Wernicke's area) and the arcuate fasciculus that connects these two areas (Ojemann 1991). Recent updates from advanced neuroimaging studies have extended this language network to include the parietal lobe and BA 47 in the inferior frontal lobe (Hagoort 2005a; Friederici 2009; Xiang et al. 2010).

F(c)MRI / DTI and functional / structural connectivity

Most of you may have seen the MRI (magnetic resonance imaging) scanner in hospitals (Figure 1.1a). Doctors use them to scan patients' anatomical structure to examine their health condition. We, as cognitive neuroscientists, use this same equipment to study functional brain activities that correspond to mental operations. This technique extends traditional anatomical imaging to include maps of human brain function. It is called fMRI (functional magnetic resonance imaging). fMRI measures the hemodynamic response (change in blood flow) related to neural activity. Based on the detected contrast of blood deoxyhemoglobin, it can produce the Blood-Oxygen-Level Dependence (BOLD) signal that can be used as a qualitative measure of brain activity.

Two neuroimaging techniques using MRI were employed to study the language networks in this thesis.

The first one is fcMRI (resting-state functional connectivity magnetic

resonance imaging). It detects temporal correlations in spontaneous BOLD signal oscillations at low frequency (<0.1 Hz) while subjects rest quietly in the scanner (Biswal et al. 1995; Gusnard & Raichle 2001). The resting state fluctuations are localized in grey matter and can be used for detecting functional coherence in the cerebral cortex. The functional coherence is termed 'functional connectivity'. Analyses of functional connectivity allow the characterization of interregional neural interactions during particular cognitive tasks or merely from spontaneous activity during rest. Distinct resting-state networks have been related to vision, language, executive processing, and other sensory and cognitive domains (Greicius et al. 2008). It also has been suggested that resting state activity can reflect the strengthened language function in the human brain (Rilling et al. 2007).

The other neuroimaging technique we used is DTI (Diffusion Tensor Imaging). DTI produces images of biological tissues weighted with the local micro structural characteristics of water diffusion (Figure 1.1b). DTI is capable of tracing structural connections between brain regions in vivo and providing quantitative measures of brain white matter organization (Le Bihan et al. 2001). The properties of the structural connections detected by DTI are termed 'structural connectivity' or 'anatomical connectivity'. This thesis used two measures to quantify the structural connectivity of the language networks. One is Nstr (number of streamlines). It is an estimation of the number of the real nerve fibres that connect different brain areas, based on the artificial reconstruction of these fibres (Behrens et al. 2003). Another one is FA (fractional anisotropy). It is a scalar measure of anisotropy of the water diffusion model as calculated from the DTI data. It is thought to reflect fibre density, axonal diameter, and myelination in white matter (Basser & Pierpaoli 1996).

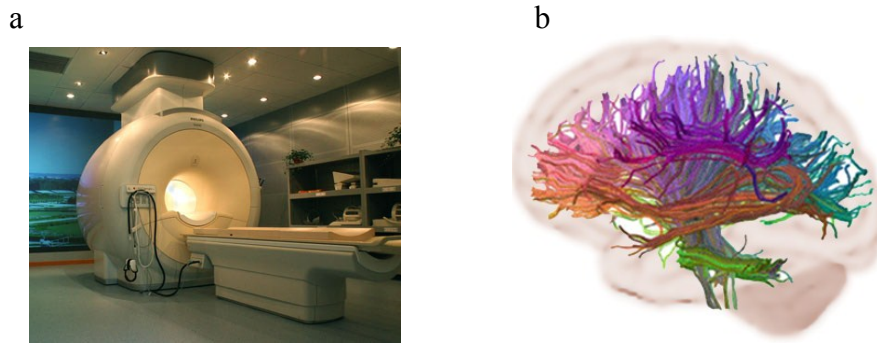


Figure 1.1 a The MRI (magnetic resonance imaging) scanner; b DTI (Diffusion Tensor Imaging) is capable of tracing structural connections between brain regions in vivo.

Graph Theoretical techniques

In this thesis we carried out the first graph theoretical analysis that focused on the structural language networks. In graph theory, a graph is a collection of dots that may or may not be connected to each other by lines. A "dot" is called a **node**. A "line" is called an **edge**. The **node degree** of a node in a graph is the number of edges that touch it. The **node centrality** of a node measures how many of the shortest paths between all other node-pairs in the network pass through it.

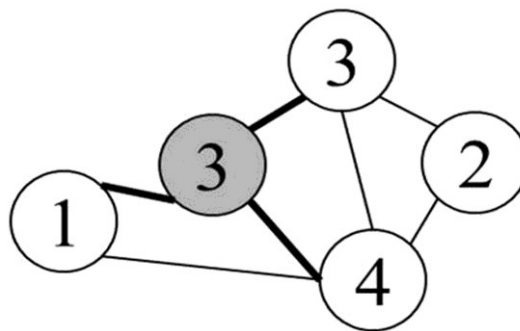


Figure 1.2 The illustration of the graph theoretical analysis. The circles represent the nodes of the graph, while the lines represent the edges. The number on each node of this graph is the node degree of that node. The vertex marked in grey has a node centrality of 2 because there are two shortest paths (the thick lines) between all other node-pairs pass through it.

Graph theory is a popular mathematical tool for representing complex data sets composed of related entities (Watts 2004). It has been applied to studies on many

natural and man-made networks such as metabolic pathways, genomics, and the structure of the World Wide Web. It has recently been largely adopted by cognitive neuroscientists for studying brain networks (Bullmore & Sporns 2009). Analyses of the large-scale structural brain networks can reveal structural cores (or hubs) that link all major structural modules (Hagmann et al. 2008). We employed this technique to study the structural language hubs.

The CNTNAP2 gene

Another novelty in this thesis is that, for the first time, we observed the effects of genes on the properties of the complex structural language networks. Numerous studies have consistently suggested the relevance of genetic factors and individual differences in brain language functions (Stromswold 2001; Ramus & Fisher 2009, review). Genes are pieces of DNA (deoxyribonucleic acid). They contain information on the order of the amino acids that is translated into proteins that build cells, tissues, and enzymes, and ultimately organisms. In this way, the genetic information at one gene ('genotype') determines the 'phenotype' (e.g. the shape of the nose). Genes are built of 'nucleotide' blocks, consisting of a sugar with a phosphate group and a base. There are four types of such bases: A (adenine), T (thymine), G (guanine), and C (cytosine). These bases are organized into pairs to form the staircase structure of DNA (and genes). The human genome includes 3.3 billion base pairs, among which there are 12 million potential variations between the genomes of two people. Differences that occur in less than one per cent of the population are called 'mutations', whereas differences that occur more frequently are called 'polymorphisms' (Attia et al. 2009).

In this thesis we focused on a common single nucleotide polymorphism (SNP)

rs7794745 of the CNTNAP2 (contactin-associated protein-like 2) gene. CNTNAP2 is down-regulated by another well-established language-related gene - FOXP2 (Vernes et al. 2008). Several studies have linked CNTNAP2 to language abilities (Alarcon et al. 2008; O'Roak et al. 2011; Poot et al. 2010; Strauss et al. 2006; Vernes et al. 2008; Whitehouse et al. 2011). A previous study by our group has discovered that CNTNAP2 affects the functional connectivity between the posterior inferior frontal and temporal language areas during language processing (Snijders et al. submitted). It is thus an important additional finding that this gene seems to influence the complex organization of the structural language networks.

Outline of the thesis

We first explored the functional organization of the language networks by investigating the functional connectivity between the inferior frontal language areas and other parts of the brain (Chapter 2). Then based on the results, we looked into the structural organization of this network and investigated how learning a new language dynamically altered the connectivity of structural language pathways (Chapter 3). Next, we investigated the relationship between the connectivity of structural language pathways and the language talents of adult individuals (Chapter 4). In Chapter 5, we employed the graph theoretical analysis to study the complex organization of the brain language networks, and looked into the effects of CNTNAP2 on the properties of the two structural hubs that approximate the classical Broca's and Wernicke's areas. Finally, in Chapter 6, I summarize the results of all these four experimental chapters and give an integrative view on the brain language networks.

Chapter 2

Topographical functional connectivity pattern in the perisylvian language network

This chapter is a slightly modified version of:

Xiang, HD, Fonteijn, HM, Norris, DG, & Hagoort, P. (2010). Topographical functional connectivity pattern in the perisylvian language networks. *Cerebral Cortex*, 20(3), 549-560.

Abstract

We performed a resting state functional connectivity study to investigate directly the functional correlations within the perisylvian language network by seeding from three subregions of Broca's complex (pars opercularis, pars triangularis and pars orbitalis) and their right hemisphere homologues. A clear topographical functional connectivity pattern in the left middle frontal, parietal and temporal areas was revealed for the three left seeds. This is the first demonstration that a functional connectivity topology can be observed in the perisylvian language network. The results support the assumption of the functional division for phonology, syntax and semantics of Broca's complex as proposed by the MUC (Memory, Unification and Control) model and indicated a topographical functional organization in the perisylvian language network, which suggests a possible division of labour for phonological, syntactic and semantic function in the left frontal, parietal and temporal areas.

Introduction

It has been suggested, based on Broca and Wernicke's classical clinical observations and many subsequent studies, that there is a neural loop that is involved in language processing (Ojemann 1991) located around the lateral sulcus (also known as the fissure of Sylvius). This is located in the dominant hemisphere (the left for most people), connected by the arcuate fasciculus. Broca's area lies at the rostral end of this loop, Wernicke's area is situated at the other end (in the superior posterior temporal lobe). The inferior parietal lobule, also known as "Geschwind's territory" (Catani et al. 2005), has also been implicated in language processing by recent neuroimaging studies. For example, several diffusion tensor imaging (DTI) studies showed that the inferior parietal lobule is connected by large bundles of nerve fibres to both Broca's area and Wernicke's area (Catani et al. 2005; Parker et al. 2005; Powell et al. 2006). Thus besides the frontal and temporal language areas, the parietal lobe is now also thought to play an important role in the perisylvian language network.

In the perisylvian language network, Broca's area is the first area of the brain to have been associated with language function (Broca 1861) and is crucial in all classical and newly developed neurobiological models of language (see review by Price 2000). For a long time, Broca's area was taken as one single unit for language processing (Nishitani et al. 2005). However, its anatomical and functional segregation has recently become a focus of attention.

Traditionally Broca's area comprises Brodmann's cytoarchitectonic areas (BA) 44 and 45, which occupy the left pars opercularis (BA 44) and pars triangularis (BA 45) of the inferior frontal gyrus in the left hemisphere. Owing to its fundamental role in language processing, especially in semantic processing (Bookheimer 2002;

Devlin et al. 2003; Hagoort et al. 2004), left BA 47 (which occupies the left pars orbitalis of the inferior frontal cortex) has recently been included as a new member of ‘Broca’s complex’. Thus, in this paper, we will use ‘Broca’s complex’ to refer to the left inferior frontal language area (including BA 44, 45 and 47) following the proposal of Hagoort (Hagoort 2005a).

The anatomical parcellation of Broca’s complex has been described in several cytoarchitectonic and DTI studies recently. BA 44 contains a thin layer IV of small granular cells with pyramidal cells from deep layer III and upper layer V intermingled with those of layer IV (“dysgranular”), BA 45 has densely packed granular cells in layer IV (“granular”) (Amunts et al. 2004). BA 47 is suggested, to be like BA 45, part of the heteromodal component of the frontal lobe, known as the granular cortex (Hagoort 2005b). The subregions in Broca’s complex were also found to have distinct external anatomical connections. Anwender and colleagues (Anwender et al. 2007) employed diffusion-tensor magnetic resonance imaging to parcellate Broca’s area by identifying cortical regions with mutually distinct and internally coherent connectivity patterns. Three subregions were discernible that were identified as putative BA 44, BA45, and the deep frontal operculum. The connectivity-based separations were found to be aligned with the macroanatomically identified boundary.

A corresponding functional division inside Broca’s complex was suggested by the functional neuroimaging studies employing language processing tasks. In his MUC (memory unification and control) model (see Hagoort 2005b), Hagoort proposed that three functional components are the core of language processing: Memory, Unification and Control, and the contribution of Broca’s complex to language processing can be specified in terms of unification operations. Broca’s

complex recruits lexical information, mainly stored in temporal lobe structures that are known to be involved in lexical processing, and unifies them into overall representations that span multi-word utterances. Based on the meta-analysis in Bookheimer (2002), Hagoort (2005a) suggested a functionally defined anterior-ventral to posterior-dorsal gradient in the left inferior frontal gyrus (LIFG). That is to say, BA 44 and parts of BA 6 have a role in phonological processing; BA 44 and BA 45 contribute to syntactic processing; and BA 47 and BA 45 are involved in semantic processing. LIFG is thus suggested to be involved in at least three different domains of language processing with a certain level of specialization in different LIFG subregions.

However, direct and comprehensive evidence for the functional parcellation of Broca's complex has not been demonstrated to date. Very recently, several DTI studies examined the functional division within Broca's complex and the perisylvian language network by investigating the anatomical connections in this network (Catani et al. 2005; Glasser & Rilling 2008). Unfortunately, it is very difficult to relate the fibres unequivocally to a given area in the cerebral cortex because DTI tracks nerve fibres (white matter) and the current limitation of the resolution of DTI technique makes it very hard to locate the end point in the grey matter.

In the present research, we performed a resting state functional connectivity study to directly investigate the functional correlations within the perisylvian language network by seeding from three subregions of Broca's complex and their homologues in the right hemisphere. Resting-state functional connectivity magnetic resonance imaging (fcMRI) detects temporal correlations in spontaneous blood oxygen level-dependent (BOLD) signal oscillations at low frequency (<0.1 Hz)

while subjects rest quietly in the scanner (Biswal et al. 1995; Gusnard & Raichle 2001). Other than the DTI technology which investigates fibres in white matter, the resting state fluctuations are well localized in grey matter and can be used for detecting functional coherence in the cerebral cortex. Distinct resting-state networks have been related to vision, language, executive processing, and other sensory and cognitive domains (Greicius et al. 2008). Furthermore, a recent comparison of resting-state brain activity in humans and chimpanzees found that humans differ from chimpanzees in showing higher levels of left-lateralized activity in frontal, temporal, and parietal regions involved in language and conceptual processing. This result suggested that resting state activity can reflect the strengthened language function in human brain (Rilling et al. 2007).

To our knowledge, this is the first systematic resting state connectivity study on the functional division of Broca's complex (including pars orbitalis) and perisylvian language network. Our results show a clear topographical functional organization in Broca's complex along with left middle frontal, parietal and temporal areas.

Methods

Subjects

Twelve right-handed healthy subjects (six females, age range 27 – 37 years) were scanned, according to institutional guidelines of the local ethics committee (CMO protocol region Arnhem-Nijmegen, the Netherlands).

MR Imaging

Subjects underwent one fMRI resting-state scan on a 3 T Siemens trio scanner, using an eight-channel phased array head coil (Invivo 8 Channel Head Array).

Resting-state data were acquired by using gradient-echo EPI with the following imaging parameters: TR = 1400 ms, flip angle = 67° to conform to the Ernst angle for this TR, TE = 30 ms, 21 slices, slice thickness 5 mm (slice gap = 1 mm), matrix size 64×64, resolution 3.5×3.5×5.0 mm, 1030 volumes, bandwidth 1815 Hz/pixel, scan time 25 min. A longer scan time (roughly four times longer than the settings commonly reported in the literatures on resting state connectivity study) was adopted to improve the sensitivity of signals. During the resting-state scans, subjects were required to stay awake with their eyes closed while avoiding any structured mental operation. All subjects were asked to confirm that they had not fallen asleep during the investigation.

Resting State connectivity analyses

Of the original 1030 fMRI volumes, the initial 6 were discarded to allow for T1 relaxation effects. All the subsequent volumes were coregistered to each other and normalized to the EPI template using routines from SPM5 (Wellcome Department of Imaging Neuroscience, University College London, UK). Non-brain structures were removed from these volumes by the BET brain extraction function in FSL (fMRIB's Software Library, <http://www.fmrib.ox.ac.uk/fsl>). Finally, spatial smoothing was applied by using a Gaussian kernel of 5 mm FWHM.

Six frontal regions (left/right pars opercularis (l-oper/r-oper), left/right pars triangularis (l-tri/r-tri) and left/right pars orbitalis (l-orbi/r-orbi)) were taken as regions of interest (ROIs) for seeding. To avoid any influence of the size of seed on the correlation results, seed regions of equal size were selected in each ROI using the 3D-VOI function of Mricron (<http://www.sph.sc.edu/comd/rorden/mricron/inde>

x.html). Based on the Automated Anatomical Labeling (AAL) template, the seed-pixels were selected by drawing three spheres (each with a radius of 2 mm) as close as possible to the centre of each ROI in the Montreal Neurological Institute (MNI) standard space. The three spheres are adjacent to each other without overlap, and together make one ROI with continuous space. The reason for using three spheres rather than one single VOI for each ROI is that irregularities in the form of the anatomical regions can be better accommodated in this way. The mean time course of each seed region (i.e. from all three spheres) was computed. Then we correlated these time-courses with all the voxels in the brain to see the functional-connectivity pattern arising from each ROI. Significance corrections for multiple comparisons were performed using a False Discovery Rate (FDR) correction ($P < 0.05$) (Genovese et al. 2002). Resting-state fMRI data is known to be dominated by very low-frequency fluctuations. Hence we filtered the time courses with a 'Butterworth filter' (band pass: 0.01 – 0.1 Hz) prior to the correlation analysis.

The correlation analyses were conducted using a random effects model in a General Linear Model (GLM) framework in SPM5. We also included in the model the mean signal time-course of the brain to exclude drift effects and the 6 motion parameters to avoid motion artefacts.

Quantitative analysis on the topology and laterality of the connectivity pattern

Based on individual data, the average connectivity (with standard errors) of each of the three left seeds to each of the three regions that constituted the observed topographical connectivity pattern in the left middle frontal, parietal and temporal

lobes (see Figure 2.2 and the results section) was computed. Using the 3D-VOI function of Mricron (<http://www.sph.sc.edu/comd/rorden/mricron/index.html>), the regions were defined as a sphere (radius: 3 mm) centred around their peak voxels (the voxel with the strongest connectivity). The connectivity strength was represented by the β coefficient of the GLM regressor of the seed. A follow-up one-way ANOVA (analysis of variance) and *post-hoc* comparisons were performed to evaluate if the difference in the connectivity strength among the three seeds in one region was significant. The same set of statistics was performed for the three right seeds and the right homologous regions in the right middle frontal, parietal and temporal areas to inspect if a similar connectivity pattern existed in the right hemisphere. A Bonferroni Correction with a threshold of $p < 0.05$ was applied to adjust for multiple comparisons.

A comparison of connectivity strength between left and right hemisphere was then performed by quantifying the laterality of the topographical connectivity pattern. The connectivity strength of each of the three left seeds to each of the three left brain regions showing topographical connectivity (i.e., left middle frontal gyrus, parietal lobe and temporal lobe; see the Results section for details) was contrasted with the connectivity strength of each of the three right seeds to each of the three right homologous brain regions (right middle frontal gyrus, parietal lobe and temporal lobe). These comparisons were performed by paired t-tests (2 tails). The connectivity strength of one seed to one region was represented by the strongest connectivity between the seed and the region. For example, the connectivity strength of l-oper to left temporal lobe was represented by the connectivity strength of l-oper to left superior temporal gyrus.

Results

General connectivity pattern of the six seed regions

Significant correlations ($p < 0.05$, FDR corrected; cluster criterion: 5 voxels) in the brain were found for all six seed regions. Figure 2.1 shows the connectivity maps of the six seeds.

Of the six seeds, l-oper and r-oper have similar connectivity patterns throughout the brain. Both of them connected significantly with a large number of clusters in the frontal, parietal, occipital and temporal lobes. L-tri and r-tri were found to have overlapping connectivity in both hemispheres (left/right pars opercularis/precentral gyrus, left posterior middle/inferior temporal gyrus, left insula, right supramarginal/postcentral gyrus), but l-tri showed significant correlation with many more and larger brain areas (as can be seen in Figure 2.1 and Table 2.2). L-orbi was found to be correlated with many areas, including right pars orbitalis, bilateral pars opercularis/triangularis, bilateral middle frontal gyrus (MFG), left angular gyrus (AG), left inferior parietal lobule, bilateral pITG, left temporal pole, left insula, bilateral putamen and left supplementary motor area (SMA). However, areas connected with l-orbi appeared much smaller than those connected with l-oper or l-tri. R-orbi only correlated with bilateral pars orbitalis and right MFG/SFG (superior frontal gyrus) and caudate/putamen.

Table 2.1 (for l/r-oper), Table 2.2 (for l/r-tri) and Table 2.3 (for l/r-orbi) give the anatomical locations and MNI coordinates of the clusters showing significant correlations.

Table 2.1 Specification of clusters connected with left/right pars opercularis

	l-oper		r-oper	
	MNI <i>p</i>	T <i>p</i>	MNI	T <i>p</i>
<i>Left hemisphere</i>				
Pars opercularis	-50 13 18	20.18	-52 15 8	5.53
Pars triangularis	-41 36 19	6.53	-44 37 22	8.19
pars orbitalis	-45 43 -14	4.33		
Precentral gyrus	-45 10 39	6.08	-54 10 36	8.82
MFG (BA 8/6)	-27 9 59	6.71	-33 47 28	5.82
SMG/postcentral gyrus	-47 -33 58	7.98	-63 -39 35	8.21
SMG/superior temporal gyrus	-63 -18 17	8.38	-59 -30 10	19.05
Superior/inferior parietal lobule (BA 7/40)	-38 -46 56	6.13	-32 -49 50	5.49
Posterior temporal lobe (BA 39/37/21/22)	-53 -64 17	9.35	-59 -59 -3	4.50
Temporal pole	-50 16 -16	5.75	-52 16 -13	5.12
Insula/putamen	-38 7 3	5.05	-35 0 -2	5.76
<i>Right hemisphere</i>				
Pars opercularis	49 18 33	6.85	54 15 13	20.64
Pars triangularis	52 27 29	6.44	40 28 25	4.11
pars orbitalis	52 40 -4	4.67	42 46 -5	5.00
Precentral gyrus	50 10 48	7.09	49 6 43	5.73
MFG (BA 46)	40 8 56	5.16	45 42 26	9.47
Postcentral gyrus	57 -8 30	5.39	19 -33 64	4.35
SMG/Postcentral gyrus	49 -31 49	4.47	59 -32 45	9.35
Superior/inferior parietal lobule (BA 7/40)	38 -49 59	4.42	42 -52 56	9.24
Occipital lobe cuneus (BA 19)	40 -74 25	3.44	36 -79 36	3.50
pSTG/pMTG	67 -42 12	6.43		
pITG/pMTG (BA 37)	60 -51 -12	3.46	63 -55 -6	4.87
aSTG (BA 21)	60 -2 -8	5.74	58 -9 1	4.40
Insula/putamen	43 -6 1	3.70	37 17 -10	9.18
<i>SMA</i>	6 15 52	6.44	2 17 55	7.48

Table 2.2 Specification of clusters connected with left/right pars triangularis

	l-tri		r-tri	
	MNI <i>p</i>	T <i>p</i>	MNI <i>p</i>	T <i>p</i>
<i>Left hemisphere</i>				
Pars triangularis	-48 30 20	19.43	-43 28 19	6.44
Pars opercularis	-41 13 34	8.36	-55 15 8	6.46
Precentral gyrus			-49 14 38	6.64
Pars orbitalis	-46 41 -4	5.60		
MFG (BA 6)	-38 5 53	6.00		
MFG (BA 8/9)	-26 12 61	5.00		
SMG/postcentral gyrus	-45 -30 51	5.07		
Superior/inferior parietal lobule (BA 7/40)	-50 -47 49	7.13	-56 -41 48	7.43
pMTG/pITG (BA 37/21)	-57 -48 -6	5.64	-62 -56 9	6.67
Insula	-31 25 0	4.80		
Putamen	-20 1 -2	4.34	-13 8 3	5.38
<i>Right hemisphere</i>				
Pars triangularis	55 33 24	7.81	52 30 18	17.71
Pars opercularis	43 15 36	7.93	43 15 34	5.73
Precentral gyrus			47 10 51	7.69
MFG (BA 8/6)	36 4 57	6.00		
Pars orbitalis			29 28 -14	5.0
SMG/postcentral gyrus			62 -42 36	4.19
Lateral middle/temporal gyrus (BA 20/21)	64 -44 -2	5.60		
pMTG (BA 37)			60 -44 5	4.54
Caudate/Putamen			17 7 12	4.85
<i>SMA</i>	-4 30 57	5.90	8 16 63	7.30

Table 2.3 Specification of clusters connected with left/right pars orbitalis

	l-orbi		r-orbi	
	MNI <i>p</i>	T <i>p</i>	MNI <i>p</i>	T <i>p</i>
<i>Left hemisphere</i>				
Pars orbitalis	-35 41 -4	12.09	-34 38 -7	6.00
Pars opercularis/triangularis (BA 44/45/48)	-32 26 26	5.78		
MFG (BA 46)	-31 37 19	6.19		
MFG (BA 8)	-30 21 31	7.23		
AG	-38 -54 34	5.57		
pITG (BA 37/20)	-46 -47 -4	5.06		
Temporal pole	-36 27 -24	4.48		
Caudate/Putamen	-15 17 16	7.24		
<i>Right hemisphere</i>				
Pars orbitalis	38 40 5	5.61	34 38 -3	20.87
MFG/SFG (BA 48/46)			31 45 7	7.78
MFG (BA 46)	21 19 31	4.79		
pMTG (BA 37)	41 -28 -3	4.76		
Caudate/Putamen	19 14 7	5.01	15 6 10	6.04
<i>SMA</i>	-2 30 61	5.42		

Note: In Tale 2.1-2.3, the Montreal Neurological Institute coordinate (MNI_p) and T value (T_p) of the peak voxel, anatomical location and comparison of volume (the volume connected with left pars opercularis (l-oper) vs. the one connected with right pars opercularis (r-oper)) are given for each cluster. The threshold used is $p < 0.05$, FDR corrected (cluster criterion: 5 voxels). MFG: Middle frontal gyrus; SMG: Supramarginal gyrus; pSTG: posterior superior temporal gyrus; aSTG: anterior superior temporal gyrus; SMA: Supplementary motor area; pMTG: posterior middle temporal gyrus; pITG: posterior inferior temporal gyrus; SFG: Superior frontal gyrus; AG: Angular gyrus.

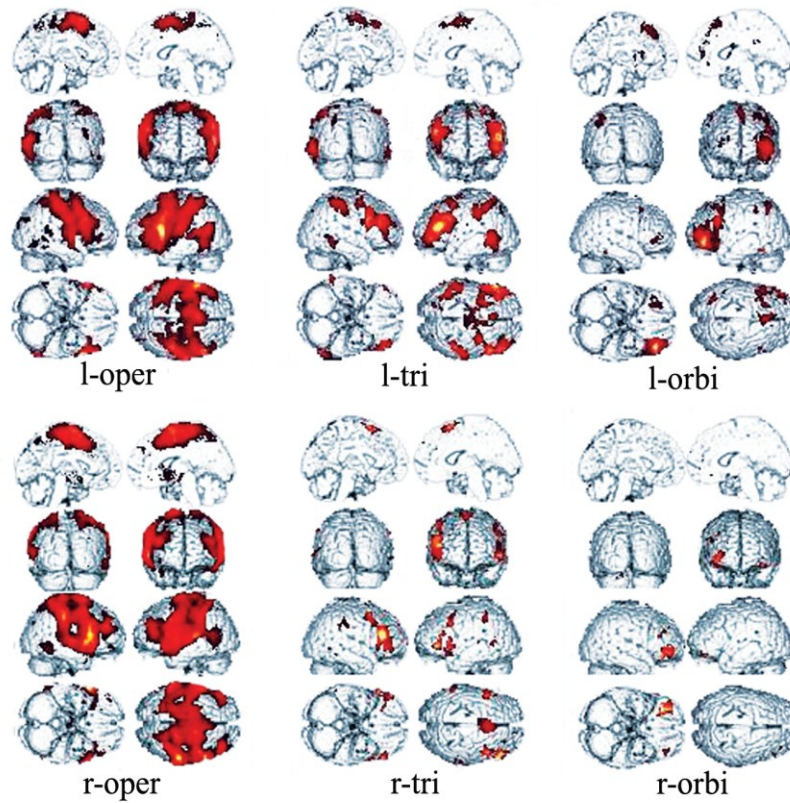


Figure 2.1 Resting state connectivity pattern of six frontal seed regions across the whole group of subjects ($p \leq 0.05$ FDR-corrected), overlaid on SPM5 standard brain in MNI space. L-oper, l-tri, l-orbi, r-oper, r-tri, and r-orbi represent the connectivity pattern to left pars opercularis, left pars triangularis, left pars orbitalis, right pars opercularis, right pars triangularis, and right pars orbitalis respectively.

The observed topographical connectivity pattern of the three left seed regions

When the connectivity maps of all the six seed regions were overlaid in one window, a structured gradient topography of the connectivity pattern of the three left seeds was found in left MFG, left temporal lobe and left parietal lobe. But no topographical connectivity pattern was found for the three right seeds at the current threshold. Figure 2.2 shows the topographical gradient in the left frontal seed regions (around left pars opercularis, pars triangularis and pars orbitalis), left MFG, temporal and parietal lobes.

Around the seeding area, all three left seeds show strong connectivity with the ROIs from which they originated (this is also indicated in Table 2.1, Table 2.2 and Table 2.3). Overlap among the three connectivity maps was found in all three seed regions. Particularly, a substantial overlap between the connectivity maps of l-oper and l-tri was found inside pars triangularis.

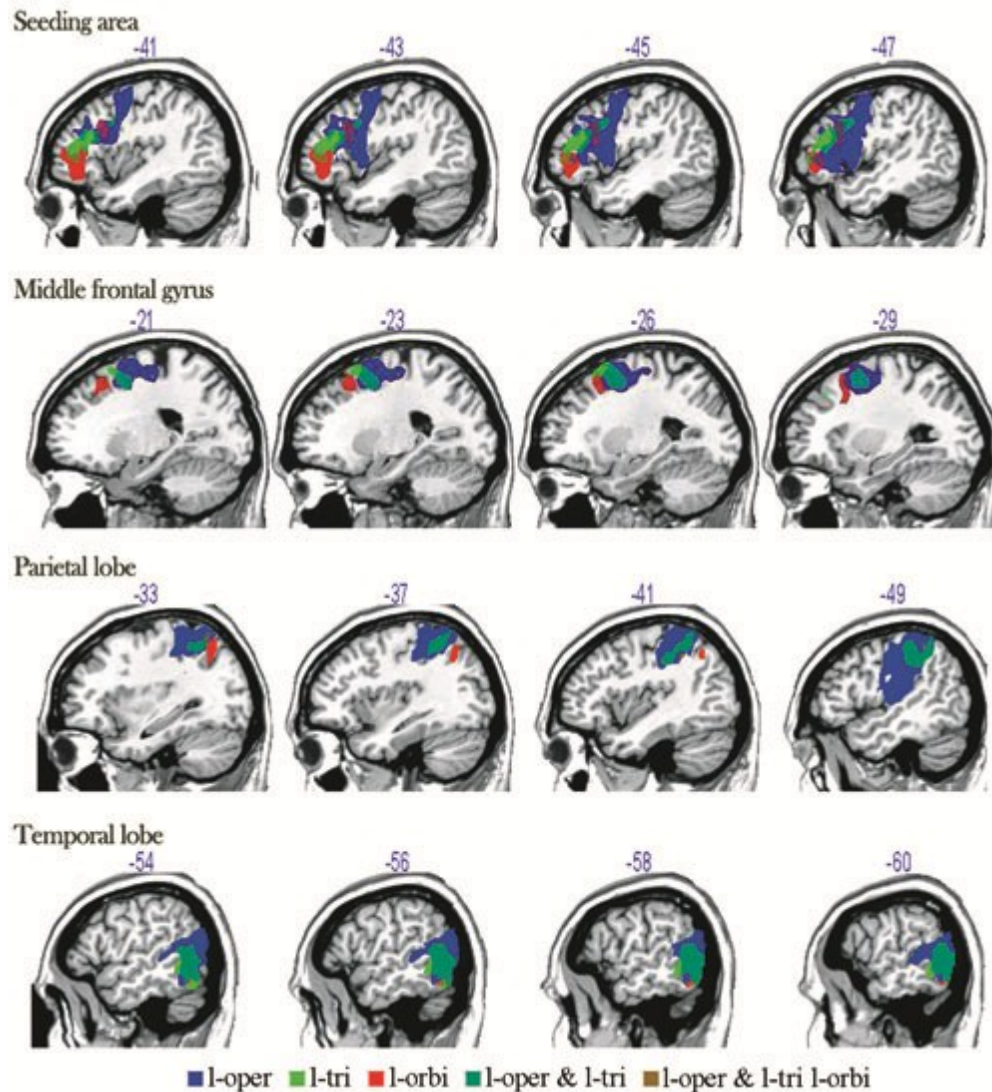


Figure 2.2 The topographical connectivity pattern in frontal, temporal and parietal lobe of the three left seeds. L-oper, l-tri and l-orbi represent the connectivity pattern to left pars opercularis, left pars triangularis and left pars orbitalis respectively. ‘&’ indicates the overlapping connectivity pattern to the two or three seeds. Above each image the MNI coordinate index is shown in blue. For the sake of a better presentation, the threshold for the connectivity map of seeding area is set to $p < 0.02$ FDR-corrected, which is a little bit more conservative than the threshold used for the connectivity map of left MFG, temporal lobe and parietal lobe ($p < 0.05$ FDR-corrected).

In left MFG (approximately BA 8/6/46), l-oper shows significant correlation with the posterior superior part (approximately BA 8/6), while l-orbi exhibits a significant correlation with the anterior inferior part (approximately BA 46). The area connected with l-tri lies between areas connected with l-oper and l-orbi, and has a large overlap with the region connected with l-oper and small overlap with the region connected with l-orbi.

In left parietal lobe, l-oper correlates with the superior and anterior parts of the superior and inferior parietal lobules, SMG and postcentral gyrus. L-orbi correlates with the posterior and inferior parts of the superior and inferior parietal lobule (adjacent to and overlapping with AG). The area connected with l-tri lies right between the connectivity maps of l-oper and l-orbi in the superior and inferior parietal lobule, with a large overlap with the area connected with l-oper.

In left temporal lobe, l-oper correlates largely with the posterior superior temporal gyrus (pSTG) and the superior part of the posterior middle temporal gyrus (pMTG), and also extends to pITG. L-tri correlates with pMTG and extends to pSTG and pITG, which overlaps with and is somewhat inferior to those areas connected with l-oper. L-orbi only correlates with pITG, which lies in the most inferior part of the temporal region.

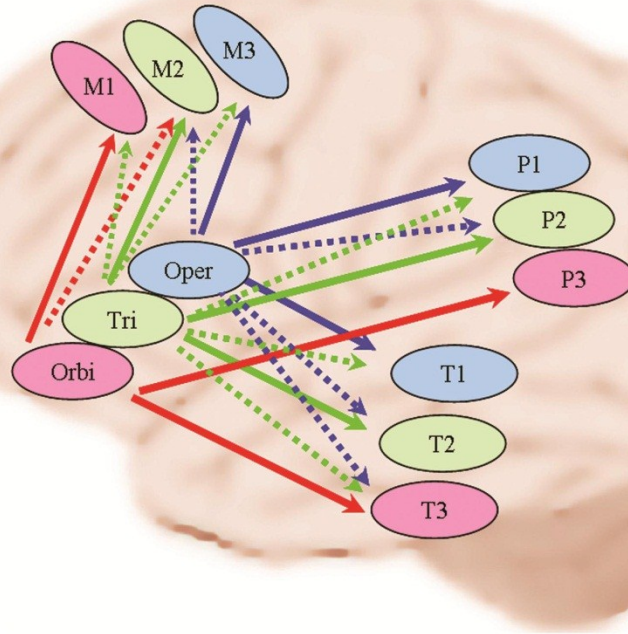
A sketch of the topographical connectivity pattern can be seen in Figure 2.3a.

The quantitative topology and laterality of the topographical connectivity pattern

In Figure 2.3b, the average connectivity (with standard errors) of each of the three left seeds to each of the three regions that constituted the observed

topographical connectivity pattern in the left middle frontal, parietal and temporal lobe is presented.

a



b

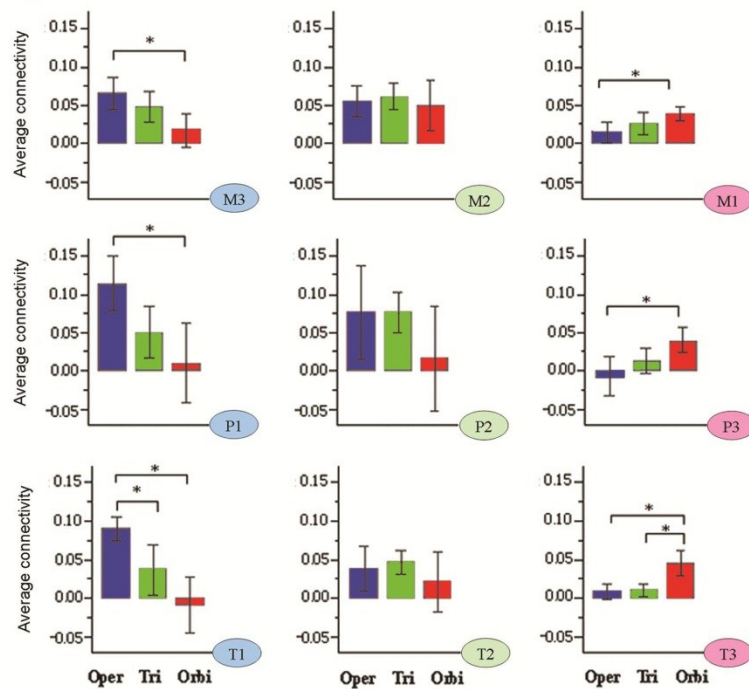


Figure 2.3 a The topographical connectivity pattern in the perisylvian language networks. Connections to the left pars opercularis (oper), pars triangularis (tri) and pars orbitalis (orbi) are shown with blue, green and red arrows respectively. The solid arrows represent the highest

connectivity and the dashed arrows represent the overlapping connections. Brain areas assumed to be mainly involved in phonological, syntactic and semantic processing are shown in light blue, light green and light red circles respectively (for details on the function and interaction of these brain areas, refer to the Discussion section). b The average connectivity (with standard errors) of each of the three left seeds to each of the three regions that constituted the observed topographical connectivity pattern in the left middle frontal, parietal and temporal lobes. M1: the anterior inferior part of MFG; M3: the posterior superior part of MFG; M2: the MFG area between M1 and M3; P1: superior and anterior part of the superior and inferior parietal lobules; P3: area adjacent to and overlapping with AG; P2: the area between P1 and P3 in the superior and inferior parietal lobules; T1: pSTG and superior pMTG; T2: inferior pMTG; T3: pITG. Oper, Tri or Orbi represents each of the three left seeds. ‘*’ indicates significant difference ($p < 0.05$ Bonferroni corrected) in the connectivity strength between two seeds in that brain region.

Significant differences in the connectivity strength between l-oper and each of the other two left seeds were found in T1 (pSTG and superior pMTG). Similar significant differences were found between l-orbi and each of the other two left seeds in T3 (pITG). In M1 (the anterior inferior part of MFG), P1 (superior and anterior part of the superior and inferior parietal lobules), M3 (the posterior superior part of MFG) and P3 (area adjacent to and overlapping with AG), significant differences were detected between l-oper and l-orbi.

Significant differences in the connectivity strength between l-oper and each of the other two left seeds were found in T1 (pSTG and superior pMTG). Similar significant differences were found between l-orbi and each of the other two left seeds in T3 (pITG). In M1 (the anterior inferior part of MFG), P1 (superior and anterior part of the superior and inferior parietal lobules), M3 (the posterior superior part of MFG) and P3 (area adjacent to and overlapping with AG), significant differences were detected between l-oper and l-orbi.

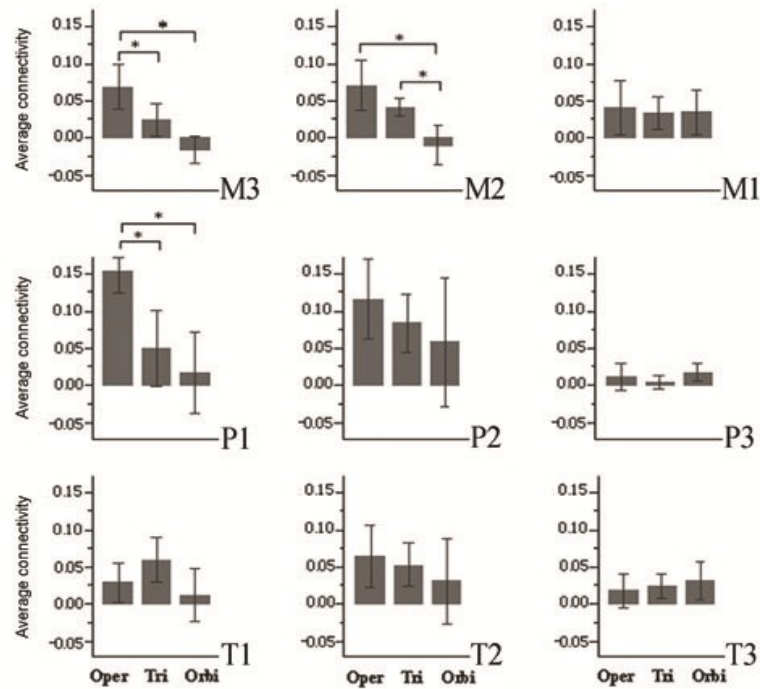


Figure 2.4 The average connectivity (with standard errors) of each of the three right seeds to each of the three right homologous regions in the right middle frontal, parietal and temporal lobes. M1: the anterior inferior part of MFG; M3: the posterior superior part of MFG; M2: the MFG area between M1 and M3; P1: superior and anterior part of the superior and inferior parietal lobules; P3: area adjacent to and overlapping with AG; P2: the area between P1 and P3 in the superior and inferior parietal lobules; T1: pSTG and superior pMTG; T2: inferior pMTG; T3: pITG. Oper, Tri or Orbi represents each of the three right seeds. ‘*’ indicates significant difference of the connectivity strength between two seeds in that brain region.

Although all the other comparisons were not significantly different, the average connectivity of each seed to those regions showed a gradient consistent with the topographical connectivity pattern shown in Figure 2.2 and depicted in Figure 2.3a. In M3, P1 and T1, l-oper shows the highest average connectivity; l-tri shows less; l-orbi is the lowest. In M1, P3 and T3, on the contrary, l-orbi shows the highest average connectivity; l-tri shows less; l-oper is the lowest. While in M2 (the MFG area between M1 and M3), P2 (the area between P1 and P3 in the superior and inferior parietal lobules) and T2 (inferior pMTG), l-tri shows the highest average connectivity; l-oper shows less; l-orbi is the lowest.

Table 2.4 The contrasts of connectivity between left and right hemisphere

	Middle frontal		Posterior temporal		Parietal lobe	
	T	<i>p</i>	T	<i>p</i>	T	<i>p</i>
Oper	-0.24	0.82	3.58*	0.004	-2.02	0.07
Tri	1.96	0.08	-0.38	0.71	-0.31	0.76
Orbi	0.42	0.68	1.34	0.21	2.85*	0.02

T and *p* represent the T value and *p* value of the 2-tailed paired t-test respectively. A positive T value indicates stronger connectivity in the left hemisphere than in the right hemisphere. A negative T value means weaker connectivity in the left hemisphere than in the right hemisphere. *: significant results ($p < 0.05$).

In the right hemisphere (see Figure 2.4), a similar gradient of the average strength was observed only in M3, P1 and T3. Significant differences were detected between r-oper and each of the other two right seeds in M3 and P1.

The results of the comparison of the connectivity strength between left and right hemisphere are shown in Table 2.4. The connectivity between pars opercularis and posterior temporal lobe (to be more precise, pSTG and the superior part of pMTG) and the connectivity between pars orbitalis and parietal lobe (adjacent to and overlapping with AG) in the left hemisphere are significantly stronger than those in the right hemisphere.

Discussion

Explanation for general connectivity patterns

Seeding from Broca's complex, significant correlations were found to many brain regions including, but not exclusively the traditional perisylvian language loop (see Table 2.1, Table 2.2 and Table 2.3). Broca's area has been suggested to have a central role in coordinating time-sensitive perceptual and motor functions

underlying verbal and nonverbal communication and is involved in various functions (see review by Judas & Ceganec 2007). Thus it is not surprising to find significant connectivity not only to previously suggested phonological, syntactic and semantic areas (such as posterior superior/middle/inferior temporal gyrus, SMG, AG and insula), but also to the sensory/motor areas (such as pre/post- central gyrus, SMA and caudate/putamen).

The left topographical connectivity pattern and its functional division

What is most interesting among the present results is the topographical connectivity pattern of Broca's complex within the left middle frontal, parietal and temporal areas. This functional connectivity result is consistent with the results of previous functional language studies.

We used Broca's complex (including pars orbitalis) instead of the traditional Broca's area as our seed regions in the present study because pars orbitalis has been found to play an important role in language (especially semantic) processing. As reviewed by Hagoort et al. (in press), the activation of BA 47 and BA 45 have been consistently found to be activated across semantic studies employing different design paradigms. These studies either compared sentences containing semantic/pragmatic anomalies with their correct counterparts (Hagoort et al. 2004; Newman et al. 2001; Kuperberg et al. 2000, 2003, 2008; Ni et al. 2000; Friederici et al. 2003; Ruschemeyer et al. 2006), or compared sentences with and without semantic ambiguities (Hoenig & Scheef 2005; Rodd et al. 2005; Zempleni et al. 2007; Davis et al. 2007).

As mentioned in the Introduction, the MUC model suggested an anterior-ventral to posterior-dorsal functional gradient in Broca's complex: BA 44

for phonological processing, BA 44 and BA 45 for syntactic processing, and BA 47 and BA 45 for semantic processing. The assumption was mainly based on the recent meta-analysis of neuroimaging language studies by Bookheimer (2002). However, the observation of similar results in language studies is not new. Poldrack et al. (1999) conducted a literature search in an attempt to find all brain imaging studies employing task comparisons designed to isolate semantic, phonological, or lexical processing. They characterized each task comparison in terms of several different categories: semantic decision (e.g., living–nonliving decision), semantic production (e.g., verb generation), lexical retrieval (i.e., word/nonword decision, word-stem completion), phonological processing (e.g., phoneme monitoring or nonword processing), overt speech (e.g., word repetition or naming), and silent viewing of words. Their review demonstrated that the posterior and dorsal region of the left inferior frontal cortex (corresponding to BA44/45) was specialized for phonological processing, and the ventral and anterior region of the left inferior frontal cortex (approximating to BA 47/45) was preferentially active during the performance of tasks requiring overt semantic processing. Besides these brain imaging studies, direct cortical stimulation of area 44 in patients undergoing surgical removal of the epileptic focus disrupts phoneme monitoring even when patients were not required to articulate (Ojemann & Mateer 1979). Another study using chronically implanted depth electrodes in BA 47 found greater activity in that region related to semantic decision relative to a perceptual decision (Abdullaev & Bechtereva 1993). Existing results on the study of syntactic processing highlight the role of pars triangularis for syntax. Musso et al. (2003) reviewed the studies on syntactic processing in their discussion and concluded that pars triangularis has an ‘indisputable and essential’ function for the processing of syntactic aspects of language. Since activation in pars

triangularis in syntactic processing was found to be independent of the language (English, Chinese, German, Italian or Japanese) of subjects (Hahne & Friederici 1999; Friederici et al. 2000; Embick et al. 2000; Ni et al. 2000; Sakai et al. 2002), they suggested that this brain region is specialized for the acquisition and processing of hierarchical (rather than linear) structures, which represents the common character of every known grammar. Furthermore, a meta-analysis of functional neuroimaging studies of syntactic processing (Indefrey 2004) reported that the most replicable finding related to syntactic parsing across imaging techniques, presentation modes, and experimental procedures, was the activation localized in left BA 44 and 45, consistent with what is known from brain lesion data (Caramazza & Zurif 1976; Friederici 2002).

Thus, by seeding from the three subregions of Broca's complex in this study, we expected to discover a connectivity pattern that is consistent with these previous results: pars opercularis (corresponding to BA 44) mainly correlates with brain areas for phonological processing and also extends to brain regions for syntactic processing; pars triangularis (corresponding to BA 45) mainly correlates with brain areas for syntactic processing and also extends to brain regions for phonological and semantic processing; while pars orbitalis mainly correlates with brain regions involved in semantic processing. Our results are indeed consistent with those assumptions. Details are given in the following paragraphs.

In left temporal lobe, l-oper correlates largely with pSTG and the superior part of pMTG, and also extends to pITG. L-tri correlates with pMTG and extends to pSTG and pITG, which overlaps with and is somewhat inferior to those areas connected with l-oper. L-orbi only correlates with pITG. In functional neuroimaging

studies, activations related to phonological/phonetic properties have been mostly reported for the central to posterior superior temporal gyrus extending into the superior temporal sulcus (Binder et al. 1997, 2000; Cannestra et al. 2000; Castillo et al. 2001; Jancke et al. 2002; McDermott et al. 2003; Indefrey & Cutler 2005; Scott & Johnsrude 2003; Aleman et al. 2005; Papanicolaou et al. 2006), activations related to semantic information have been mostly found to be distributed in the left middle and inferior temporal gyri (Vandenberghe et al. 1996; Binder et al. 1997, 2000; Cannestra et al. 2000; Price 2000; Castillo et al. 2001; Hickok & Poeppel 2004; Poeppel et al. 2004; Damasio et al. 1996; Saffran & Sholl 1999; Billingsley et al. 2001; Gitelman et al. 2005; Indefrey & Cutler 2005). Although the neural substrates of syntactic processing within the temporal lobe have not been consistently located, pMTG has been shown to be activated in syntactic tasks and supports processing of sentence structure (Stowe et al. 1998; Cooke et al. 2002; Constable et al. 2004; Snijders et al. 2008). Besides, activation of pSTG has also been found in relation to syntactic complexity (constable et al. 2004) and grammatical violation (Embick et al. 2000).

Recently, Hagoort et al (in press) suggested an interesting distinction of function between superior temporal and inferior frontal areas. The superior temporal gyrus was observed to have a higher activation level in response to a congruent sounds and images/letters combination as compared to an incongruent combination (Van Atteveldt et al. 2004; Beauchamp et al. 2004; Hein et al. 2007), while inferior frontal area showed a stronger response when matching incongruent sounds and images/letters (Hein et al. 2007). It was argued that these results suggested a possible division of labour between inferior frontal and superior temporal areas, with a stronger contribution to integration for superior/middle temporal cortex and a

stronger role for the inferior frontal cortex in unification. Integration occurs when different sources of information converge to a common memory representation. This part of cortex is more strongly involved in conditions with a congruent input, resulting in converging support for a pre-stored representation. Unification refers to a constructive process in which a semantic or syntactic representation is constructed that is not already available in memory. This is always harder for more complex or incongruous input (Hagoort et al. in press). Combining these previous functional neuroimaging results and the present connectivity results, we suggest that the unification component for each linguistic modality (phonology, syntax or semantics) in the inferior frontal cortex has a corresponding integration/memory component in the posterior temporal cortex, and these two corresponding components are highly correlated with each other. To summarize, posterior superior/middle temporal cortex and pars opercularis (mainly) /triangularis for phonological integration and unification respectively; posterior middle temporal cortex and pars triangularis (mainly) /opercularis for syntactic integration and unification respectively; posterior inferior (mainly) /middle temporal cortex and pars orbitalis (mainly) /pars triangularis for semantic integration and unification respectively. This connectivity pattern is illustrated in Figure 2.3a.

In left parietal lobe, l-oper was found to be correlated with both SMG and the postcentral gyrus. L-orbi mainly correlated with the brain regions adjacent to and overlapping with AG. The area connected with l-tri lies right between the connectivity maps of l-oper and l-orbi in the superior and (mainly) inferior parietal lobule. Patients with left parietal lesions have been noted to have deficits in auditory short-term memory (Saffran & Marin 1975; Warrington and Shallice 1969).

Functional imaging studies have implicated the same area in tasks accessing the phonological store in working memory (Jonides et al. 1998; Cabeza & Nyberg 2000). Particularly, the function of left parietal lobe for phonological processes (e.g. mapping orthography to phonology, phonological recoding, rhyme detection etc.) seems mainly to involve SMG (Paulesu et al. 1993; Demonet et al. 1992, 1994; Price 1998; Pugh et al. 2001; Seghier et al. 2004). In contrast, AG has been observed to be mostly involved in semantic processing (Demonet et al. 1993, 1994; Binder 1997; Lurito et al. 2000; Price 2000; Binder et al. 2005; Sabsevitz et al. 2005). Lesion studies of patients with alexia have proposed that the posterior portion of the reading network in the left cerebral hemisphere involves functional links between AG and extrastriate areas in occipital and temporal cortex associated with the visual processing of letter and word-like stimuli. AG is also thought to have functional links with posterior language areas (e.g., Wernicke's area) and is presumed to be involved in mapping visually presented inputs onto linguistic representations (see review by Horwitz 1998). Few reports have been published on the syntactic function of the parietal lobe. However, a parietal area responsible for the omission of syntactic-morphological markers has been consistently identified in two patients in a cortical electrical stimulation mapping study (Bhatnagar et al. 2000). This parietal area is presumably in the region between SMA and AG (see Figure 1.1 and Figure 1.2 in the results section of Bhatnagar et al. 2000) though the authors did not precisely name it in their report. A functional neuroimaging study (Embick et al. 2000) also found a so-called "AG/SMG" region which was more activated by ungrammatical sentences than sentences containing spelling errors. The coordinates reported by the authors for the centre of this "AG/SMG" region lies right inside the parietal area connected with l-tri in the present study. Combining

previous research with our functional connectivity results, again shows the similar topographical connectivity pattern in left parietal lobe: l-oper is mainly correlated with brain areas for phonological processing (SMG) and l-orbi is correlated with brain regions for semantic processing (AG). Based on the reports from the cortical electrical stimulation mapping and neuroimaging studies, we hypothesize that the areas connected with l-tri in the superior and inferior parietal lobule may have a function in syntactic processing. Further precisely designed studies are needed to test this hypothesis.

The topographical connectivity pattern and its functional division in the parietal lobe suggests a different explanation for the ‘Geschwind’s territory’ that was discovered by Catani et al. (2005) in their DTI study on perisylvian language connectivity. Beyond the classical arcuate pathway connecting Broca's and Wernicke's areas directly, they found an indirect pathway passing through a region of inferior parietal cortex, which they called the ‘Geschwind’s territory’. Catani et al. interpreted the indirect pathway and the Geschwind’s territory as subserving semantic processing. However, their figures (mainly Figure 1.2) show that the focus of the so called ‘Geschwind’s territory’ is in SMG, which in the present results, along with pSTG, shows a very strong connectivity to left pars opercularis. Thus the present results suggest that the Geschwind’s territory is more likely to be involved in phonological rather than semantic processing.

In left MFG, l-oper has significant connectivity with the posterior superior part (approximately BA 8/6), l-orbi shows significant correlation with the anterior inferior part (approximately BA 46), while l-tri mainly reveals strong connectivity in the middle part (between areas connected with l-oper and l-orbi). MFG

(approximately BA 9/8/6/46) is also known as the dorsolateral prefrontal cortex (DLPFC), and has been associated with aspects of executive control. Activations of this area are typically observed in tasks that require maintenance and manipulation of information in working memory (see Miller 2000 for a review). In the language domain, it has been found to be involved in verbal action planning and intentional control (Roelofs & Hagoort 2002) and the control of language switching in bilinguals (Abutalebi et al. 2008; van Heuven et al. 2008). However, little is known about the functional division of MFG from language studies. Based on the connectivity pattern in the left temporal and parietal lobe, our results tentatively suggest that MFG is also topographically organized and displays a gradient of functional organization in which the posterior superior MFG is more involved in phonological control, the anterior inferior MFG is more involved in semantic control, and the middle part between the two areas is more involved in syntactic control. In spite of sparse evidence from language research, the functional division of MFG has been mainly studied in researches on cognitive control. Based on the research results in this field, Koechlin and colleagues (Koechlin et al. 2003) proposed a cascade model on the architecture of cognitive control in the lateral prefrontal cortex (LPFC). This model postulated that the LPFC was organized as a hierarchy of representations and processed distinct signals involved in controlling the selection of appropriate stimulus-response associations. Specifically, it hypothesized that cognitive control involved at least three nested levels of processing, implemented in distinct LPFC regions. Interestingly, the topographical connectivity pattern in MFG in the present study reveals a similar corresponding hierarchical anatomy as the suggested architecture in LPFC for the three levels of cognitive control in the cascade model. This may indicate a close correspondence

between the general cognitive function and the specific language processing in MFG. Given that fcMRI can probe connectivity, but not function, we do not wish to make any specific claims regarding the functional division of MFG.

It should be noticed that there is much overlap between the connectivity patterns of the three seed regions, even though the foci of the connectivity maps are separable. In the present results, overlap of the connectivity pattern can be found inside Broca's complex itself and also in the left middle frontal, parietal and temporal lobe where the topographical connectivity pattern was found. This is consistent with previous results of functional imaging studies. Bookheimer (2002) has concluded in her review article that the subregions of the inferior frontal gyrus form a network of unique but highly interactive, compact modules which give rise to the tremendously complex language processing of which humans are capable. The MUC model also claims that the overlap of activations for the three different types of information is substantial and suggests the possibility of interactive concurrent processing in which various types of processing constraints are incorporated as soon as they become available. Particularly in the topographical connectivity pattern found in the present study, the connectivity pattern of l-tri was always found to have a large overlap with that of l-oper, which suggests substantial functional interactions between these two regions. Several DTI studies consistently report that both left pars opercularis and pars triangularis connect with parietal and temporal association cortices by a dorsal pathway via the arcuate and the superior longitudinal fasciculi (Catani et al. 2005; Anwander et al. 2007). However, left pars orbitalis seems to be connected to temporal cortex by a ventral pathway via the uncinate fascicle (Anwander et al. 2007). Figure 2.3a summarizes the topographical

connectivity pattern and those interactions in Broca's complex, MFG, parietal lobe and temporal lobe.

It is also interesting to notice that the main findings of the present study can be interpreted within the framework of the MUC model (Hagoort 2005b). As being mentioned in the Introduction section, the MUC model suggested three functional components to be the core of language processing: Memory, Unification and Control. Broca's complex is proposed as the 'unification area' and is thought to be at the heart of the combinatorial nature of language. Unification refers to the integration of lexically retrieved information into a representation of multi-word utterances and the integration of meaning extracted from non-linguistic modalities. The memory component refers to the different types of language information stored in long term memory and the retrieval operations, which includes the phonological/phonetic properties of words, their syntactic features and their conceptual specifications. The left temporal lobe was suggested to be the 'memory area'. The control component was assumed to account for the fact that the language system operates in the context of communicative intentions and actions, and was suggested to have a neural base in MFG (DLPFC) and ACC (Anterior Cingulate Cortex). In the present research, we do discover a strong correlation to the 'memory area' and the 'control area' (MFG in the present study) by seeding from the 'unification area'. And the connectivity pattern in the 'memory area' and the 'control area' is consistently topographically and functionally organized according to the subregions we seeded in the 'unification area'. This is also consistent with the functional division as what has been suggested in the Model itself. However, our results revealed that the parietal lobe also correlated strongly with the 'unification

area', but its involvement in the language processing is not yet described by the MUC model.

The different strength of the connectivity pattern

In both hemispheres, the largest connectivity pattern was observed for pars opercularis and the smallest connectivity pattern was seen for pars orbitalis. Pars triangularis showed less connectivity than pars opercularis but more than that of pars orbitalis. This difference in connectivity strength is not likely to be caused by the size of seed regions because equal seed regions were selected in each region in the present research. The percentage of white/grey matter included in the seed regions also is not likely to affect the results because we chose the seeds from the central region of each ROI and computed the mean time courses of each seed region for the correlation analysis. Thus this difference in connectivity strength seems to reflect the intrinsic differences in the strength of the functional connections in the perisylvian language network. Consistently, it is interesting to notice that several recent DTI studies on language networks discovered strong anatomical connections among SMG, Broca's area and Wernicke's area (Catani et. al. 2005; Parker et. al. 2005), which could well correspond to our connectivity pattern for pars opercularis (maybe also partly correspond to the connectivity pattern for pars triangularis because there is great overlap between the connectivity pattern of pars opercularis and pars triangularis). However, to our knowledge, no such report on the connection among pars orbitalis, AG and pITG has been made.

The laterality of the connectivity pattern

When the connectivity maps of all the six seed regions were overlaid in one window, the structured gradient topography of the connectivity pattern was only found in the left hemisphere. No such topographical connectivity pattern was found in the right hemisphere at the threshold we used (FDR corrected $p < 0.05$). Further comparisons of the strength of the topographical connectivity pattern between the two hemispheres revealed several significant differences. The connectivity between pars opercularis and the temporal lobe (particularly, pSTG) and the connectivity between pars orbitalis and the parietal lobe (particularly, AG) in the left hemisphere were significantly stronger than those in the right hemisphere. Greater fronto-temporal connectivity on the left has been found by Powell et al. (2006) when they used MR tractography to demonstrate the structural connections of the cortical regions activated by expressive and receptive language tasks. They proposed that this structural asymmetry reflects the left-sided lateralization of language function in the human brain.

As a whole, the left lateralized topographical connectivity pattern probably suggests that the left hemisphere layout follows a more functionally parcellated segregation of language function than the right hemisphere. It indicates that the left hemisphere may become more specialized for the language function than the right hemisphere in evolution.

Conclusion

We used fcMRI to infer the functional organization of Broca's complex and the perisylvian language network by investigating their functional correlations. A clear topographical functional connectivity pattern in the left middle frontal, parietal and temporal areas was revealed when seeding from the three subregions (pars

opercularis, pars triangularis and pars orbitalis) of Broca's complex. The results are consistent with previous studies on the language function of brain. They support the assumption of the functional division for phonology, syntax and semantics of Broca's complex as proposed by the MUC model, and indicated a topographical functional organization and division of labour for phonological, syntactic and semantic function in the left frontal, parietal and temporal areas.

Chapter 3

L2-proficiency-dependent laterality shift in structural connectivity of brain language pathways

This chapter is a slightly modified version of:

Xiang, HD, van Leeuwen TM, Dediu D, Roberts L, Norris DG, Hagoort P. (in preparation). "L2-proficiency-dependent laterality of structural connectivity of brain language pathways".

Abstract

Using Diffusion Tensor Imaging, we investigated whether the achieved L2 (second language) -proficiency during L2 acquisition could be explained by the reorganization of structural connectivity between core language areas. We found that, with increasing L2 proficiency, the hemispheric dominance of the BA6-Temporal pathway (mainly along the arcuate fasciculus) shifts from the left to the right hemisphere in the initial learning stage. With increased proficiency, however, the dominance is again found in the left BA6-Temporal pathway. This result resonates with the generally-recognized phenomena in behavioural and functional neuroimaging studies on L2 acquisition. This is the first time that a L2-proficiency-dependent laterality shift in structural connectivity of language pathways during L2 acquisition has been observed. It suggests that structural connectivity in (at least part of) the perisylvian language network may be subject to fast dynamic changes following language learning.

Introduction

Second language (L2) learning is of increasing importance in the globalized world, but as yet we know little about the neural underpinnings of language acquisition. The neural substrate of language learning has been largely studied by investigating functional plastic changes in the brain; recent studies have shown that learning languages causes structural changes at least in the parietal and posterior temporal lobe. Moreover, the degree of reorganization seems to be modulated by L2 proficiency (Richardson & Price 2009 review). For instance, Mechelli et al. reported that L2-learning increased the grey matter density in the left inferior parietal cortex. The degree of structural reorganization in this region is modulated by the proficiency attained and the age of acquisition (Mechelli et al. 2004). These results have been replicated by Osterhout et al. in 2008 (Osterhout et al. 2008).

Although currently reported structural plastic changes following L2-learning are limited to certain brain regions, human language processing is known to employ brain networks involving multiple areas (Price 2010). Early anatomically based models of the language network (i.e., the so called 'perisylvian language network') consisted of Broca's area, Wernicke's area and the arcuate tract that connects these two areas (Ojemann 1991). Recent updates on the perisylvian language network take into account of the contribution of the parietal lobe and anterior temporal areas (Catani et al. 2005; Hagoort 2005a; Xiang et al. 2010). The traditional Broca's area (Brodman Area [BA] 44, 45) was suggested to be extended to a larger Broca's complex that also includes part of BA6 and BA47 (Hagoort 2005a). Several recent studies have shown that areas in the parietal and posterior temporal lobes are both functionally and anatomically connected to subregions of Broca's complex (Xiang et al. 2009; Friederici 2009 review). In light of the available evidence, we hypothesize

that structural change as a result of language learning not only occurs in a few isolated brain regions, but is reflected in the connectivity between important brain areas in the language network. This is consistent with fast dynamic changes in structural connectivity that have been reported by many studies on working memory and other short-term training, and clinical or animal experiments (Johansen-Berg et al. 2010 review). For example, Scholz et al. detected a localized increase in structural connectivity following 6-week training of juggling (Scholz et al. 2009). Therefore, the present study aims to investigate whether learning a second language induces changes in structural connectivity between Broca's complex and parietal and posterior temporal regions. We were particularly interested to see whether the achieved L2-proficiency during learning could be explained by the reorganization of structural connectivity between core language areas.

Another well-known fact concerning the neural substrates of language is that brain function for language is lateralized. Functional language lateralization to the left hemisphere is found in 95% of right-handers (the majority of the population) and to the right-hemisphere in 15% of left-handers (Pujol et al. 1999; Lurito & Dzemidzic 2001). A recent meta-analysis on 23 laterality studies revealed that monolinguals and late bilinguals showed reliable left hemisphere dominance (Hull & Vaid 2006). Functional imaging studies on L2 learning have also observed a L2-proficiency-dependent lateralization of brain activation for L2 processing during learning. Right-handed low-proficiency L2 learners were found to show complete right- to weak left-lateralized activation during L2 (vs. L1) processing; while high-proficiency L2 speakers activated largely the same left-lateralized brain areas as during L1 processing (Perani et al. 1996; Dehaene et al. 1997). In other words, the language function of the majority of monolinguals and bilinguals is left

lateralized before any L2 learning occurs. The language function appears to be right lateralized (at least for L2 processing) when individuals are at a low level of L2 proficiency and then returns to being left lateralized when individuals have achieved a greater level of proficiency in the L2. In the present study, we investigated if such a L2-proficiency-dependent brain lateralization also exists in the structural connectivity of the perisylvian language network. Diffusion Tensor Imaging (DTI) was employed to study language pathways and their structural connectivity. DTI produces images of biological tissues weighted with the local micro structural characteristics of water diffusion, which is capable of tracing structural connections between brain regions in vivo and providing quantitative measures of brain white matter organization (Le Bihan et al. 2001). DTI was reported to be able to precisely measure neuroanatomical changes in the strength and in fibre myelination with learning and development (Casey 2002).

Methods

Participants and procedures

The data reported in the present research includes two samples. One sample consisted of 13 participants (3 males). The other sample comprised 24 participants (4 males). Participants for both samples were healthy, right-handed German students (18-20 years old). All are late (post-puberty) bilinguals. They came to the Netherlands to pursue a college/university education after having finished their high-school studies in Germany. They undertook a 6-week intensive Dutch-learning course (20 hours classroom-instruction per week) after arrival in the Netherlands. Immediately after the course, they were required to pass the national Dutch test in order to be qualified as college/university candidates.

At two time points (before and after the course), we acquired DTI scans for each participant, and used a cloze test (supplementary material) to measure their proficiency in Dutch, taken from the national proficiency in Dutch test (<http://www.expertisecentrum.nl/>). This test is an assessment consisting of a short text with certain words removed, where the participant is asked to fill in the gaps with the correct words. In addition, all participants were required to fill out a questionnaire to ensure that they had similar language backgrounds. All gave written informed consent and the study was conducted according to institutional guidelines of the local ethics committee (CMO protocol region Arnhem-Nijmegen, The Netherlands).

DTI parameters

The scanning of the participants in Sample 1 was done on a Siemens 1.5 T Avanto scanner with the following parameters: echo planar imaging (EPI) sequence, repetition time (TR) = 9900 ms, echo time (TE) = 88 ms, 60 diffusion directions defined evenly across the sphere with a diffusion weighting of $b = 700 \text{ s/mm}^2$, 64 slices, matrix = 128 x 128, FOV = 320 x 320 mm², isotropic voxels of 2.5 mm³.

The scanning of participants in Sample 2 was performed on a Siemens 3 T Trio scanner with the following parameters: echo EPI sequence, TR = 10500 ms, TE = 94 ms, 110 diffusion directions defined evenly across the sphere with a diffusion weighting of $b = 1000 \text{ s/mm}^2$, 70 slices, matrix = 110 x 110, FOV = 220 x 220 mm², isotropic voxels of 2.0 mm³.

DTI data analysis

DTI datasets were preprocessed by the DTI toolbox developed at the Donders Institute for Brain, Cognition and Behaviour (Zwiers, 2009). The probabilistic tractography technique of FSL (Behrens et al. 2003) was employed to trace the possible pathways between left parietal lobe (seed region) and each of the four subregions of Broca's complex (i.e., left BA6, BA44, BA45 and BA47, as the target region), respectively. To investigate the laterality of these pathways, the same tractography was applied to the right homologous regions. The possible pathways between posterior temporal lobe (seed) and each of the four subregions of Broca's complex (target) were traced in the same way. Seed regions were drawn based on our previous study on the topographical functional connectivity pattern of the perisylvian language network (Xiang et al. 2010). Brain regions in the parietal lobe or posterior temporal lobe that showed significant functional connectivity to Broca's complex were taken as regions of interest (ROI). Voxels in these ROIs were then dilated (i.e., extended) with a radius of 4 mm under the restriction of not exceeding the boundaries of the parietal or posterior temporal lobe. The purpose of the dilation is to better accommodate the endpoints of fibre bundles. Target regions were defined according to the AAL (Automated Anatomical Labeling) template (Tzourio-Mazoyer et al. 2002). An exclusion mask of the sagittal midline was also implemented in the tractography to remove pathways that cross into the other hemisphere. The pathways were visualized with the help of MRICron (<http://www.cabiatl.com/mricro/mricron/index.html>).

Two DTI measures were adopted to describe the structural connectivity properties of the traced pathways: Nstr (number of streamlines) and FA (fractional

anisotropy). The probabilistic tractography repetitively samples from the distributions of voxel-wise principal diffusion directions, each time computing a streamline from the distribution on the location of the true fibre connections. Nstr counts how many such samples of streamlines succeed from the predefined seed region to the predefined target region (Behrens et al. 2003). Nstr is an estimation of the number of the real fibres based on the artificial reconstruction of these fibres. It should be kept in mind that Nstr (represented by a parameter called ‘waytotal’ in FSL) is not a straightforward measure of tract integrity. It has been suggested that normalized values of waytotal should be used to avoid a possible tractability bias caused by subject motion or scanner noise. FA is a measure reflecting directional organization of water diffusion that is greatly influenced by the magnitude and orientation of white matter tracts. It is thought to reflect fibre density, axonal diameter, and myelination in white matter (Basser & Pierpaoli 1996). To avoid subjective thresholding, a probability-weighted average FA was calculated for each pathway and subject using the following equation (derived from: (Hua et al. 2008)):

$$\text{Mean FA} = \sum(\text{Pr}_i * \text{FA}_i) / \sum \text{Pr}_i \quad 1$$

Where Pr_i is the probability of the i th voxel to be part of the reconstructed tract, empirically decided by the number of streamlines that pass through the i th voxel divided by the total number of streamlines.

To assess the structural laterality of each connection, lateralization indices (LI) were calculated for both Nstr and FA using the following equation:

$$\text{LI} = (\text{Left} - \text{Right}) / (\text{Left} + \text{Right}) \quad 2$$

In this way, a more positive value indicates ‘more left-lateralized’ and a more negative value means ‘more right-lateralized’. The scale runs from -1 (completely right lateralized) to 1 (completely left lateralized).

Correlation and regression analysis for proficiency in Dutch and structural connectivity profiles

Using SPSS 16.0 (*SPSS, Inc., Chicago IL*), 2-tailed t-tests were employed to compare the difference in cloze score before the course and after the course. Correlation and regression analyses were used to investigate the relationship between proficiency in Dutch and connectivity profiles. The first several steps were carried out by a stepwise regression analysis.

First, we investigated whether improvements of proficiency in Dutch may be explained by changes in connectivity profiles of certain pathways, or alternatively, related to connectivity profiles of certain pathways before the course. Changes in proficiency in Dutch, Nstr, and FA were calculated by subtracting the value before the course from the value after the course. Improvements on cloze score (Cloze_dif) were regressed on changes in Nstr (Nstr_dif), Nstr before the course (Nstr_bef), and the lateralization index (LI) of Nstr_dif (LI_Nstr_dif) and Nstr_bef (LI_Nstr_bef). Time differences between the scanning date and course starting/ending dates, time between the two scans (Date_after_course - Date_before_course), and Sample (the sample to which the subject belonged) were entered as control regressors. The summation and changes of summation of left and right Nstr (Sum_Nstr_bef and Sum_Nstr_dif) for each pathway were also included as regressors to control for brain size and the bias of tractability caused by subject motion or scanner noise.

It is worth noting that the proficiency in Dutch and the connectivity profiles labelled 'before the course' do not necessarily represent the baseline of 'zero' Dutch learning. About half of our participants were scanned 1-4 days after the course started due to the time pressure on the scanning schedule (most participants did not arrive in the Netherlands until 1-3 days before the course started). Also several participants reported in the questionnaire that they had some type of formal or informal instruction of Dutch before the course started. However, it is difficult to quantify the learning effects based on the learning time they reported because of the mixed effects of informal and formal learning. Thus in the present study, cloze score is taken as the only index of proficiency in Dutch (see Discussion for more details).

First, we performed a correlation analysis on cloze scores and the results revealed a significant high correlation between Cloze_dif and Cloze score before the course (Cloze_bef) (See Results for more details). It suggested the possibility that any relationship we may observe between Cloze_dif and connectivity profiles might be indirectly caused by the relationship between Cloze_bef and connectivity profiles. That is why Cloze_bef was added as a specific regressor to investigate this possibility.

Second, we investigated whether individual variances in proficiency in Dutch before the course may be explained by the connectivity profiles of certain pathways before the course. Cloze_bef was regressed on Nstr_bef and LI_Nstr_bef of each traced pathway. The time difference between the scanning date and the course starting date, the data sample number and Sum_Nstr_bef were entered as control regressors.

The same analysis steps were carried out to investigate the relationship between cloze score and FA.

Further analyses on BA6-Temporal pathway

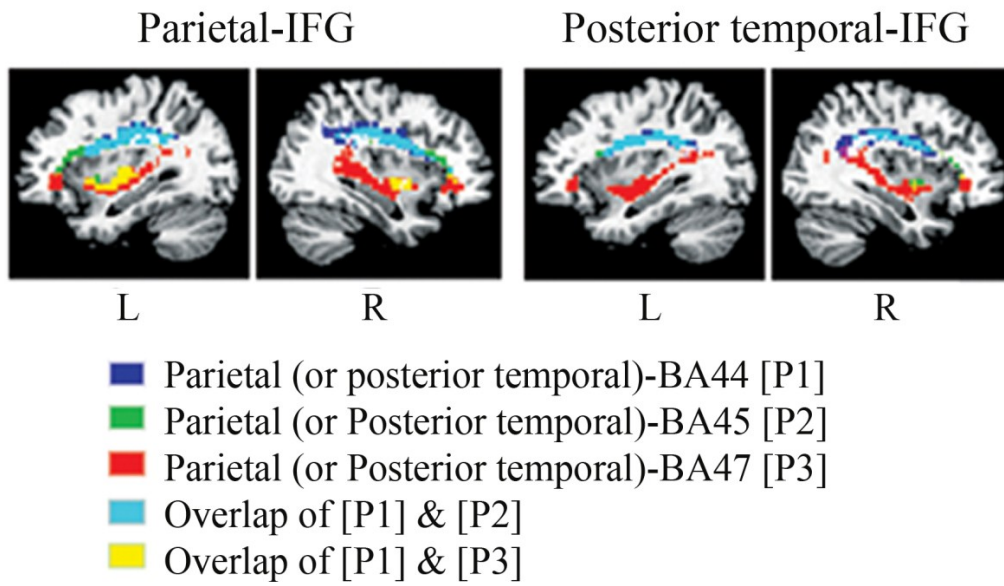
Based on the results of the regression analyses, 2-tailed t-tests were employed to compare the difference before the course and after the course for connectivity profiles of the BA6-Temporal pathway. Bivariate correlation analysis was used to investigate the relationship between cloze scores and connectivity profiles (Nstr & LI_Nstr) of this pathway.

Based on the results of the correlation analysis, a 'curve estimation' regression analysis was employed to investigate whether there is a non-linear relationship between cloze scores and connectivity profiles. Logarithmic, inverse, quadratic and cubic equations were tested in this regression analysis. Data acquired both before and after the course were combined to be the input of the regression model. The relationship between cloze scores and the lateralization index, and the relationship between cloze scores and the normalized Nstr of left or right BA6-Temporal pathway were investigated. Nstr was normalized by using left or right Nstr divided by the summation of left and right Nstr. The purpose of normalization is to reduce the bias of tractability caused by subject motion or scanner noise (as mentioned previously), and to improve the curve estimation.

Results

DTI fibre tractography discovered robust structural connections for all seed-target pairs in 97% of the participants (Figure 3.1). While connections between the parietal or posterior temporal lobe and BA6 or BA44 are observed to mainly lie in the dorsal part of the brain, connections between these two lobes and BA 47 go through the ventral part. Connections between the same two lobes and BA 45 are seen in both dorsal and ventral parts of the brain.

a



b

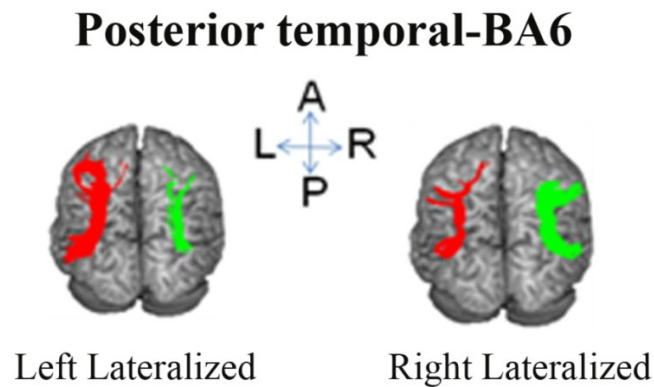


Figure 3.1 a Sagittal view of traced pathways between parietal/posterior temporal lobe and 3 subregions (BA44, 45 and 47) of IFG (Broca's complex). b Left/right lateralized BA6-Temporal pathways projected on the MRICRON brain template, with left pathways in red and right ones in green. L: Left hemisphere; R: right hemisphere; A: anterior brain; P: posterior brain.

All participants scored higher on the Dutch cloze test after the course compared to before the course ($t(36) = 12.72, p < 0.0001$). There is a high negative correlation between Cloze_bef and Cloze_dif ($r = 0.89, p < 0.0001$) and positive correlation between Cloze_bef and Cloze_aft ($r = 0.50, p = 0.002$), see Figure 3.2.

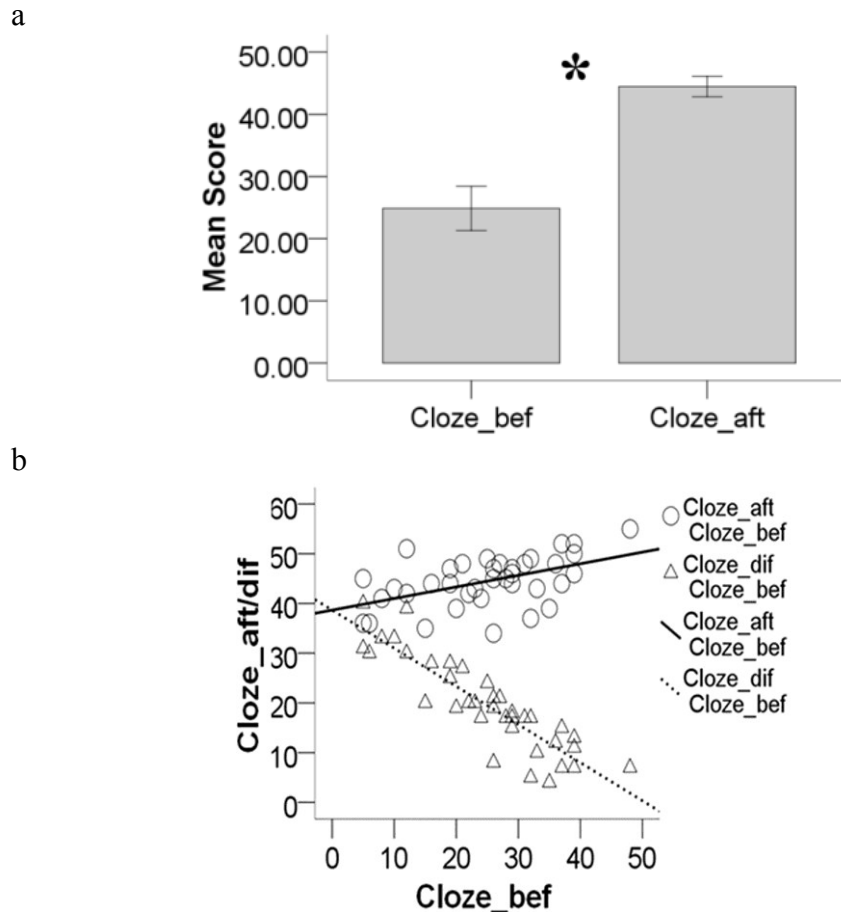


Figure 3.2 a Comparison between cloze score before the course (Cloze_bef) and cloze score after the course (Cloze_aft); b Correlations between Cloze_bef and Cloze_aft and cloze score improvements (Cloze_dif). *: $p < 0.0001$.

The step-wise regression analyses for Cloze_dif found the most optimal model for both Nstr (adjusted $R^2 = 0.80$, $p < 0.0001$) and FA (adjusted $R^2 = 0.78$, $p < 0.0001$). Table 3.1 shows the detailed results for regressing Cloze_dif on Nstr or FA of all traced pathways, Cloze_bef and other control variables. Cloze_bef is the largest or only predictor in both models ($b = -0.84$ for Nstr and $b = -0.89$ for FA). These results consistently suggest that Cloze_dif is largely influenced by Cloze_bef. Thus it is the relationship between Cloze_bef and connectivity profiles before the course that should primarily be investigated.

Table 3.1. Parameters of the most optimal models for cloze score improvements

	Standardized Coefficients	
	Nstr	FA
Cloze_bef	-.84***	-.89***
R44T_dif	.17*	n.s.

*: $p < 0.05$; ***: $p < 0.0001$; Cloze_bef: cloze score before the course; R44T_dif: changes of Nstr on the right BA44-Temporal pathway.

The step-wise regression analysis for Cloze_bef found the most optimal model for Nstr (adjusted $R^2 = 0.17$, $p = 0.006$). But no model was found for FA. As shown in Table 3.2, LI6T_bef (Lateralization Index of Nstr BA6-Temporal pathway measured before the course) was suggested to be the best predictor for Cloze_bef ($b = -0.44$). Therefore this pathway was investigated in further detail.

Table 3.2 Parameters of the most optimal model for cloze score before the course

	Standardized Coefficients
LI6T_bef	-.44**

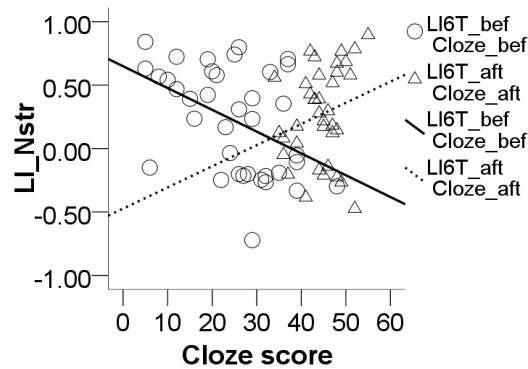
.: $p < 0.01$; *.: $p < 0.0001$; LI6T_bef (Lateralization Index of Nstr BA6-Temporal pathway measured before the course).

Results for BA6-Temporal pathway

An interesting qualitative difference was found between the correlation of Nstr with cloze scores before the course and the correlation of Nstr with cloze scores after the course. Before the course, there was a significant negative correlation ($r = -0.44$, $p = 0.006$) between cloze scores and LI6T (LI of BA6-Temporal pathway). While after the course, the correlation turned into a positive trend ($r = 0.23$, $p = 0.17$), as shown in Figure 3.3a. Similar contradictory trends were observed on Nstr of both left and right BA6-Temporal pathways, as demonstrated in Figure 3.3b. Nstr_L6T (Nstr of the left BA6-Temporal pathway) showed a trend of negative

correlation with cloze score before the course, but a trend of positive correlation with cloze score after the course.

a



b

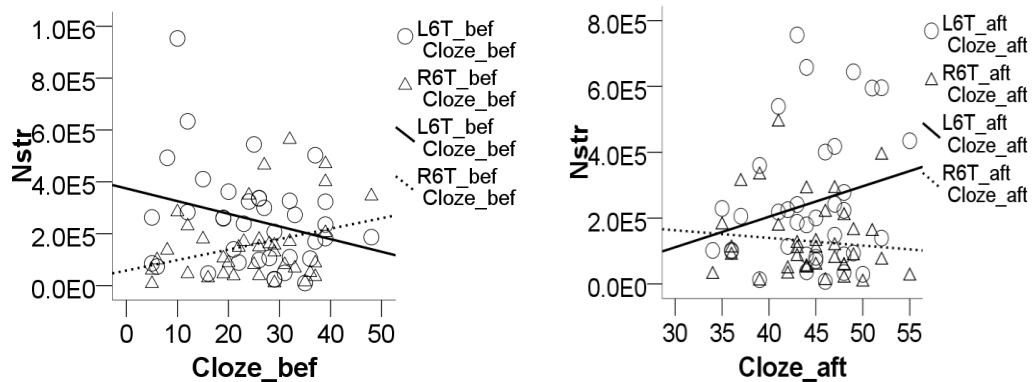
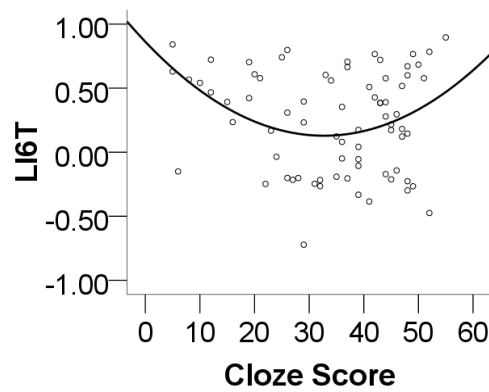


Figure 3.3 Qualitatively different correlations of cloze scores and LI_Nstr (a) or Nstr (b) of BA6-Temporal pathway between before the course and after the course. Nstr shows the number of reconstructed fibres. LI6T: LI of BA6-Temporal pathway; L6T: Nstr of left BA6-Temporal pathway; R6T: Nstr of right BA6-Temporal pathway; bef: measurement before the course; aft: measurement after the course.

In contrast, the opposite pattern was observed in the right hemisphere. Nstr_R6T ((Nstr of the right BA6-Temporal pathway) showed a trend of positive correlation with cloze score before the course, but a trend of negative correlation with cloze score after the course.

a



b

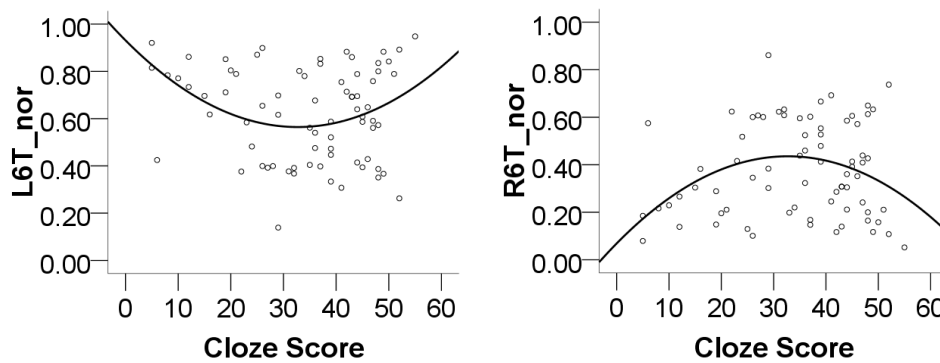


Figure 3.4 Correlations between cloze scores and the LI (a) and normalized Nstr (b) of BA6-Temporal pathway as explained by a Quadratic equation. LI6T: Lateralization Index of BA6-Temporal pathway; L/R6T_nor: normalized Nstr of left/right BA6-Temporal pathway.

'Curve fits' revealed significant correlations between cloze scores and the LI/Nstr of BA6-Temporal pathway as explained by a Quadratic equation (adjusted $R^2 = 0.08$, $p = 0.02$, for all 3 models). Model parameters are shown in Table 3.3. As revealed in Figure 3.4a, a shift in LI6T was observed: With increasing cloze scores, LI6T shifts from left- to right- and then back to left-lateralized. Figure 3.4b reveals the Quadratic correlation between normalized Nstr and cloze scores: Normalized Nstr of L6T first decreases with the increasing cloze score, then returns to the

original level; Normalized Nstr of R6T first increases with increasing cloze score, then falls to the original level¹.

Table. 3.3 Parameters of the Quadratic equation models on BA6-Temporal pathway.

	Standardized Coefficients		
	LI6T	L6T	R6T
Cloze_score	-1.479**	-1.479**	1.479**
Cloze_score ²	1.403**	1.403**	-1.403**

*: $p < 0.01$; ***: $p < 0.001$. LI6T: Lateralization Index of Nstr BA6-Temporal pathway; L6T: Nstr left BA6-Temporal pathway; R6T: Nstr right BA6-Temporal pathway.

Discussion

Anatomical connections in the perisylvian language network

Our fibre tracking results are generally in agreement with previous findings on language pathways (Catani et al. 2002; Friederici 2009). The dorsal pathways (BA6, 44 and part of BA45 – Parietal and Temporal pathways) in our results may well represent the four components of the superior longitudinal fasciculus (SLF) (Makris et al. 2005). SLF includes a superior portion consisting of horizontal fibres that connect the superior parietal lobe (SLF-I), the angular gyrus (SLF-II) and the supramarginal gyrus (SLF-III) to ipsilateral frontal and opercular areas. The inferior portion consists of long arched fibres that connect the superior and middle temporal gyri with frontal ipsilateral areas (SLF-IV). This inferior portion is also termed the arcuate fasciculus (AF). The dorsal temporal-frontal pathways we found are also proximate to the direct segmentation' of AF described by Catani et al; the dorsal

¹ 2-tailed t-tests did not reveal any significant differences between before the course and after the course on both Nstr and FA of the left or right BA6-Temporal pathway. Neither did the lateralization indices of Nstr and FA on this pathway show such a difference. It is probably due to the fact that the comparisons of means cannot capture the dynamic changes.

parietal-frontal pathways we found seem to correspond to the “anterior segment” of the indirect Broca-to-Wernicke pathway running parallel to the main AF described by Catani et al (Catani et al. 2007).

The ventral posterior temporal-frontal pathways (BA47 and part of BA45 – Temporal pathways) go along the extreme capsule, part of which connects the inferior frontal gyrus (IFG) and the middle-posterior portion of the superior temporal gyrus (STG) (Makris & Pandya 2009). The ventral pathways between parietal lobe and frontal lobe (i.e., (BA47 and part of BA45 – Parietal pathways in the present results) have been described in the dissection of the superior fronto-occipital fasciculus by Catani et al (Catani et al. 2002). The medial parts of the ventral parietal/posterior temporal-frontal pathways may also consist fibres of the cingulum. The cingulum runs within the cingulated gyrus all around the corpus callosum. It contains fibres of different length. Its short U-shaped fibres connect the medial frontal, parietal, occipital, and temporal lobes and different portions of the cingulated cortex (Catani and de Schotten 2008).

Cloze test as the Dutch proficiency index

The present study employed cloze tests to measure the proficiency in Dutch. Cloze tests require the ability to understand context and vocabulary in order to identify the correct words or type of words that belong in the deleted passages of a text. This exercise is commonly administered for the assessment of native and second language learning and instruction. Cloze scores were claimed to be indicators of a general language proficiency factor (Oller 1983), because they correlate well with scores of dictation, reading tests, and essay writing, as well as with standardized proficiency tests (Fotos 1991).

L2-proficiency-dependent laterality shift in structural connectivity

The most interesting result of the present study is the discovery of the L2-proficiency-dependent laterality shift in the structural connectivity between BA6 and posterior temporal lobe. With increasing cloze scores, the laterality of the BA6-Temporal pathway was found to shift from left- to right- and, in the end, back to left-lateralized. Normalized Nstr of L6T first reduces with increasing cloze score, and then returns to the original level. Normalized Nstr of R6T first increases with increasing cloze scores, then drops down back to the original level.

These results resonate with the generally-recognized phenomena in behavioural and functional neuroimaging studies on L2 acquisition: Laterality of brain activation for L2 processing shows L2-proficiency-dependent changes (shifts).

Hull and Vaid (2006) conducted a meta-analysis on behavioural studies that examined hemispheric functional asymmetry for language in monolingual and bilingual adults. 23 laterality studies that involved 1234 participants were investigated. The experimental paradigm includes dichotic listening, visual hemi-field presentation, and dual task. Their results indicated that low-proficiency bilinguals are right lateralized, while high-proficiency bilinguals are left hemisphere dominant. This claim stands when L2 is acquired after the age of 6, which is the case for participants in the present study. These authors concluded that functional organization for language may actually shift from an initial right lateralization to a later left hemisphere dominance as L2 proficiency increases, at least for late (age >6) bilinguals (Hull & Vaid 2006).

In neuroimaging studies, L2 processing has been found to activate largely the same brain areas as L1 (native language) for proficient speakers. However, less proficient L2 speakers activate a diffuse network that includes right STG and right

IFG, medial frontal cortex, and posterior parietal regions (Kelly & Garavan 2005; Perani & Abutalebi 2005). Earlier evidence has come from studies on story listening (Dehaene et al. 1997; Perani et al. 1998). High-proficiency bilinguals did not differ in their cortical activation between L1 and L2 story listening, which are both left lateralized. Low-proficiency L2 learners showed variable activations from complete right-lateralization to weak left-lateralization during L2 story listening. Story listening is a complicated task which may involve multiple aspects of language processing. More recently conducted studies that have reported a L2-proficiency-dependent functional lateralization following language learning have employed phonological tasks. For instance, a study on pitch learning reported that after training, successful learners showed increased activation in the left posterior superior temporal gyrus; while the less successful learners showed increased activation in numerous areas, including the right superior temporal gyrus and sulcus, and the bilateral medial frontal, prefrontal, inferior temporal, and parietal regions (Wong et al. 2007). In addition to many such phonological studies, it is interesting to note that a longitudinal study on artificial grammar learning (AGL) has reported a similar phenomenon in activation in IFG following learning (Newman-Norlund et al. 2006). The study reported that activation in left IFG correlated positively with improving L2 proficiency, whereas activity in the right homologue was negatively correlated with L2 proficiency.

It should be noted, that it is beyond the capability of the cloze test to measure if the participants in the low, medium, and high scoring ranges are taking the same strategies when processing L2. In other words, the changes in the structural connectivity patterns may reflect that the participants in the different scoring ranges are doing different things. It is beyond the research purpose of this Chapter to

investigate what is underlying these differences. However, it should be kept in mind that the reorganization of the structural connectivity pattern may not subserve a constant process.

Fast structural connectivity changes

The 'shift' in laterality of structural connectivity in the present results suggests that the laterality of structural connectivity may be subject to fast dynamic changes during L2 learning. Recent studies have revealed that the human brain is a highly plastic organ throughout the life span (see reviews: Buonomano & Merzenich 1998; Johansson 2004; Pascual-Leone et al. 2005; Boyke et al. 2008; Draganski & May 2008). Although the present study is the first to demonstrate such a phenomenon for language acquisition in the normal population, abundant evidence has been accumulated on fast dynamic changes in structural connectivity from studies on working memory and other short-term training, and clinical or animal experiments (Johansen-Berg et al. 2010). Scholz et al. published the first study on fast structural connectivity changes in which they detected a localized increase in FA in white matter following 6-week training at juggling (Scholz et al. 2009). Lovden and colleagues reported, that for a total of one hundred and one 1-hour sessions on a set of memory and perceptual tasks, training affected several DTI measures and increased the area of the anterior part of the corpus callosum. These alterations were found to be of similar magnitude in younger and older adults (Lovden et al. 2010). In a recent study by Takeuchi and colleagues, participants undertook 2 months of 25-minute-per-day working memory training. The amount of working memory training was found to correlate with increased FA in the white matter regions adjacent to the intraparietal sulcus and the anterior part of the body of the

corpus callosum (Takeuchi et al. 2010). Schlaug et al. investigated the connectivity strength of the arcuate fasciculus (AF) in six stroke patients with chronic aphasia, before and after an intensive period of 75–80 daily sessions of intonation-based speech therapy. All patients' speech improved after training and there was an increased number of tractography-derived fibres in right AF after therapy. A strong trend for a correlation between the change in AF fibre number and speech improvements was revealed (Schlaug et al. 2009).

One limitation of the present study is that we only measured our participants at two time points during learning. Thus we cannot directly investigate the time course of the dynamic changes of the laterality of structural connectivity for any given individual. Furthermore, what caused such a fast dynamic change in the laterality of structural connectivity remained unresolved. The reason could be the change of Nstr in either the left pathway or the right pathway, or both. We cannot draw a firm conclusion about this aspect, due to the limitation on of the current technique and methods used.

Arcuate fasciculus and BA6-Temporal pathway

In the present results, only the dorsal pathway between BA6 and posterior temporal lobe was found to show a L2-proficiency-dependent laterality shift in structural connectivity. BA6-Temporal pathway is part of AF. Most previous studies relate the role of arcuate fasciculus (AF) to supporting the dorsal phonological stream (Schmahmann et al. 2007; Duffau 2008; Frey et al. 2008; Saur et al. 2008). BA6 was also suggested to be important for phonological processing in the MUC model on neurobiology of the language function (Hagoort 2005a). An intraoperative electrical mapping study reported that stimulation at any point along the course of

AF generated reproducible phonemic paraphasias, namely disorders that affect the phonological form of the words (Duffau et al. 2002). Glasser & Rilling compared tractography results with peak activation coordinates from prior functional neuroimaging studies to assign putative functions to language pathways. They found that right AF overlapped with activation in phonological processing (bilateral) and prosodic activations (right lateralized) (Glasser & Rilling 2008). The findings are confirmatory of a right-lateralization for prosodic processing. Clinically, AF is often reported to be involved in conduction aphasia (Geschwind 1970; Tanabe et al. 1987; Geldmacher et al. 2007). It is characterized by intact auditory comprehension, fluent speech production, but poor speech repetition.

Previous studies suggest that AF plays an important role in language development by facilitating the repetition of phonological cues, and therefore aiding language learning, and speech monitoring. Consistent with the present findings, maturation of the dorsal language pathways was suggested to be highly relevant to language acquisition in studies on brain development (Zhang et al. 2007). Dorsal language pathways were also taken as the neural substrates of the phonological loop of verbal working memory. It has been suggested that this loop plays a fundamental role in the acquisition of a second language (Baddeley et al. 1988). Based on both the study of patients with lesions resulting in phonological loop deficits, and neuroimaging studies, Baddeley proposed in his working-memory model that BA6 is associated with subvocal rehearsal (Baddeley 2003; Duffau 2008). Subvocal rehearsal repeats words 'in our head' to keep verbal materials in working memory, which plays a key role in the acquisition of vocabulary (Baddeley et al. 1998). In a recent study, language-learning related activities were found to cause structural changes in the posterior temporal lobe throughout the lifespan, but they only caused

changes in the parietal lobe in teenagers (Richardson et al. 2010). The latter findings may explain why we only found correlations in dorsal temporal-frontal but not parietal-frontal pathways.

It is relevant to the present findings on L2-learning related pathways that there are inconsistencies on where the AF ends in the frontal lobe in previously published results. Due to its involvement in conduction aphasia, AF was traditionally regarded as the anatomical pathway between Broca's (BA44, 45) and Wernicke's area. However, Bernal and Ardila have argued in their recent review that the endpoints of AF mainly lie in BA6 (Bernal & Ardila 2009). For the 12 right-handed participants they studied, they found that the AF projection to Broca's area (BA44, 45) was absent in 10 participants (83.3%), and minimal in 2 (16.6%) but 100% in BA6 (Bernal & Ardila 2008). However, in a study published in the same year, Rilling et al. reported that frontal projection of AF is normally seen in BA 44 and BA 45 besides BA6 (Rilling et al. 2008). The present study also observed robust AF connections to BA44 and BA45 in most participants. The inconsistency in detecting AF's frontal lobe endpoints may be due to the different tracing algorithm employed by these studies. Rilling et al. and the present study used a newly developed algorithm (probabilistic tractography) designed to track through crossing fibres by also considering the secondary diffusion direction (Behrens et al. 2007), while Bernal and Ardila used the earlier-developed deterministic tractography (Mori et al. 1999). The limitation of deterministic tractography for detecting crossing fibres has been seen on studies investigating the right AF. Employing deterministic tractography, Catani et al reported a significant correlation between the lateralization of AF and the performance of a verbal working memory task. However, 60% of their participants were reported to have their right AFs missing

(Catani et al. 2007). Another study employed both deterministic and probabilistic tractography to trace left and right AF. Deterministic tractography identified the right AF in 34 out of 55 participants; while probabilistic tractography identified the right AF in each of the 55 participants. The authors concluded that the inability to estimate a right AF with deterministic methods did not imply a missing or even an extremely lateralized AF but instead reflected relative partial volume effects of crossing fibres in this region of the brain (Yeatman et al. 2011).

Nevertheless, the impression one can gain from the above discussion is that the BA6-Temporal connections seem to be the most robust fibre bundles that can be easily detected with both deterministic and probabilistic tractography. It also means that the tractography results may be less distorted by relative partial volume effects of crossing fibres. This could be the reason that it is the only pathway that shows significant shifting effects in lateralization in the present results as well.

Technical concerns

The present study includes two samples, which is unlikely to influence the fibre tracking results. One reason is that it was explicitly inserted as a regressor in the analysis. Another reason is, that it has been shown that DTI based reconstructions of major brain fibres are reproducible regardless of differences in data acquisition (Catani et al. 2002; Mori et al. 2002).

The L2-proficiency-dependent laterality shift in structural connectivity was only observed for measurement of Nstr but not for FA. Several other studies on the relationship between behaviour and AF also only reported correlations to Nstr but not FA (Catani et al. 2007; Lebel & Beaulieu 2009). The reason might be that AF passes through large amount of crossing fibres, which confounds the calculation of

the average FA of this pathway (Yeatman et al. 2011). Measurement of FA in regions where there are crossing fibres are found vulnerable to noise and scanning parameters. The SD (standard deviation) differences of FA were found to correspond to roughly 5–7% of the trace value in these regions, and much lower in other regions (0–2%) (Alexander et al. 2001).

Nstr is represented by the waytotal number of the probabilistic tractography in FSL in the present study. It is a relatively new DTI measure of a recently-developed advanced tracking algorithm measuring the number of streamlines of the traced pathway. Waytotal has been reported to be a good index for brain white matter properties in clinical practice. For example, it is found to be in better concordance with the clinical rating of the motor weakness than FA (Johansen-Berg & Behrens 2009). However, also waytotal may be subject to the influence of individual tractability caused by subject motion or scanner noise. Thus in the present study we use normalized values of waytotal in the 'curve fit' model to avoid this problem.

Conclusion

The present research has discovered, for the first time, a L2-proficiency-dependent laterality shift in structural connectivity of language pathways during L2 acquisition. It builds on similar findings from previous behavioural and functional neuroimaging studies, extending it to the network level. It suggests that structural connectivity in (at least part of) the perisylvian network may be subject to fast dynamic changes following language learning. It also implies that lateralization of AF should be studied with caution because it may be dependent on an individual's current learning state. Future studies with larger samples and

improved imaging and analysis techniques are expected to replicate and further investigate fast dynamic structural connectivity changes in the perisylvian language network.

Chapter 4

The structural connectivity underpinning language aptitude, working memory and IQ in the perisylvian language network

This chapter is a slightly modified version of:

Xiang, HD, Dediu D, Roberts L, van Oort E, Norris DG, Hagoort P. (invited paper:accepted). The structural connectivity underpinning language aptitude, working memory and IQ in the perisylvian language network. *Language Learning*.

Abstract

In this paper, we report the results of a study on the relationship between individual language aptitude and structural connectivity of language pathways in the adult brain, the first of its kind. We measured four components of language aptitude (*vocabulary learning*; *sound recognition*; *sound-symbol correspondence*; and *grammatical inferencing*) using the LLAMA language aptitude test (Meara, 2005). *Spatial working memory*, *verbal working memory* and *IQ* were also measured as control factors. Diffusion Tensor Imaging (DTI) was employed to investigate the structural connectivity of language pathways in the perisylvian language network. Principal Component Analysis (PCA) on the behavioural measures suggests that a general ability might be important in the first stages of second language (L2) acquisition. The results also suggest that *vocabulary learning*, *sound-symbol correspondence* and *spatial working memory* are more closely related to general *IQ* than *sound recognition* and *verbal working memory* and distinguish the tasks specifically designed to tap into L2 acquisition (*vocabulary learning*, *sound recognition*, *sound-symbol correspondence* and *grammatical inferencing*) from more generic measures (*IQ*, *spatial* and *verbal working memory*). Regression analysis suggested significant correlations between most of these behavioural measures and the structural connectivity of certain language pathways, for instance, *vocabulary learning* and BA47-Parietal pathway, *sound-symbol correspondence* and inter-hemispheric BA45 pathway, *grammatical inferencing* and BA45-Temporal pathway and BA6-Temporal pathway. These results are discussed in relation to relevant findings in the literature.

Introduction

Healthy adults differ enormously in their ability to learn foreign languages and this is one of many such examples which suggest that individual possesses different language aptitude (or ‘talent’). However, the neural underpinnings of the variation in language aptitude remain unclear. One recent study has revealed a correlation between the structural connectivity of certain language pathways and performance in a language-learning related experimental task in adults (Catani et al. 2007). However, the relationship between individual language aptitude and the structural connectivity of language pathways in the adult brain has not been directly investigated. We aimed to fill this gap by investigating the relationships between the structural connectivity of language pathways and individual performance on each of the four components of the LLAMA language aptitude test: *vocabulary learning*; *sound recognition*; *sound-symbol correspondence*; and *grammatical inferencing* (Meara, 2005). We also included *spatial working memory*, *verbal working memory* and *IQ* as controls.

Diffusion Tensor Imaging (DTI) was employed for studying language pathways and their structural connectivity. DTI produces images of biological tissues weighted with the local micro structural characteristics of water diffusion, and is capable of tracing structural connections between brain regions in vivo and providing quantitative measures of brain white matter organization (Le Bihan et al. 2001).

Methods

Participants

The data reported in the present study includes two samples. Sample 1 consisted of 15 participants (3 males) who had just graduated from high school. Sample 2 contained 20 participants (8 males) who were college/graduate students. The participants in both samples were healthy, right-handed adults between the ages of 19-26 years. All participants gave written informed consent and the study was conducted according to institutional guidelines of the local ethics committee (CMO protocol region Arnhem-Nijmegen, The Netherlands).

Behavioural tests

The LLAMA Language Aptitude Test (Meara 2005) was used to investigate the language aptitudes. It includes four computer-based sub-tests: LLAMA_B, LLAMA_D, LLAMA_E and LLAMA_F, designed to be independent of the first language (L1) of the test-taker. LLAMA_B is a *vocabulary learning* task, which measures the ability to learn relatively large amounts of vocabulary in a relatively short time. LLAMA_D is a *sound recognition* task, which tests if participants can recognize short stretches of spoken language previously presented. LLAMA_E is a *sound-symbol correspondence* task, which requires participants to work out the relationship between the sounds and the writing system based on previously heard syllables and their transliterations in an unfamiliar alphabet. LLAMA_F is a *grammatical inferencing* test that requires participants to work out the grammatical rules that operated in the unknown language. It should be noted that the LLAMA Language Aptitude Test is not a standardized test yet. However, it is becoming widely used in this field due to the convenience of its computer-based interface and independence of native language of the participants.

Three more tests of general cognitive ability were carried out. A 20-minute version of the Raven Advanced Progressive Matrices (APM) Test was employed to measure *IQ*. This timed version was shown to be an adequate predictor of the untimed APM scores (Hamel & Schmittmann 2006). A new standard computerized version of reading span test was used to test *verbal working memory* (van den Noort et al. 2008). This version uses sentence materials and requires participants to read and try to understand sentences while remembering the sentences' final word. A *spatial working memory* test which includes one forward and one backward sub-test was also conducted. This test is a computerized adaptation based on the Spatial Span subtest of the Wechsler Memory Scale— Third Edition (WMS-III; Wechsler, 1997).

In order to understand the inter-relationships between the various behavioural tasks, we performed a Principal Components Analysis (PCA). This procedure extracts a number of orthogonal components equal to the number of variables, with the first component (PC1) explaining most of the variance in the dataset, followed in decreasing order of the amount of variance explained by PC2, PC3, etc. Thus, by analysing the loadings of each of our tests on PC1, PC2, etc., we can better understand the nature of our tasks.

DTI parameters

Participants in both samples were scanned on a Siemens 3 T Trio scanner with the following parameters:

Sample 1: echo EPI sequence, repetition time (TR) = 10500 ms, echo time (TE) = 94 ms, 110 diffusion directions defined evenly across the sphere with a diffusion

weighting of $b = 1000 \text{ s/mm}^2$, 70 slices, matrix = 110×110 , FOV = $220 \times 220 \text{ mm}^2$, isotropic voxels of 2.0 mm^3 .

Sample 2: echo EPI sequence, TR = 13000 ms, TE = 101 ms, 256 directions at $b=1500$ and 24 directions at $b=0$, 70 slices, matrix = 256×256 , FOV = $256 \times 256 \text{ mm}^2$, isotropic voxels of 2.0 mm^3 .

It could be noted that Sample 2 was scanned with more advanced protocols. This is because the data of Sample 2 was acquired later than Sample 1, when the update to the currently most advanced scanning protocols in our institute was ready.

DTI data analysis

DTI datasets were processed in a similar way as in Chapter 3. They were preprocessed by the DTI toolbox developed at the Donders Institute for Brain, Cognition and Behaviour (Zwiers, 2009). The probabilistic tractography technique of FSL (Behrens et al. 2003) was employed to trace the possible pathways between the seed region in the left parietal lobe and each of the four subregions of Broca's complex (i.e., left BA6, BA44, BA45 and BA47, as the target region), respectively. To investigate the laterality of these pathways, the same tractography was applied to the right homologous regions. The possible pathways between posterior temporal lobe (seed) and each of the four subregions of Broca's complex (target) were traced in the same way. Seed regions were drawn based on our previous study on the topographical functional connectivity pattern of the perisylvian language network (Xiang et al. 2010). Brain regions in the parietal lobe or posterior temporal lobe that showed significant functional connectivity to Broca's complex were taken as regions of interest (ROI). Voxels in these ROIs were then dilated (i.e., extended) with a radius of 4 mm under the restriction of not exceeding the boundaries of the parietal

or posterior temporal lobe. The purpose of the dilation is to better accommodate the endpoints of fibre bundles. Target regions were defined according to the AAL (Automated Anatomical Labeling) template (Tzourio-Mazoyer et al. 2002). An exclusion mask of the sagittal midline was also implemented in the tractography to remove pathways that cross into the other hemisphere. The pathways were visualized with the help of MRICron (<http://www.cabiatl.com/mricro/mricron/index.html>).

Two DTI measures were adopted to describe the structural connectivity properties of the traced pathways: Nstr (number of streamlines) and FA (fractional anisotropy). The probabilistic tractography repetitively samples from the distributions of voxel-wise principal diffusion directions, each time computing a streamline from the distribution on the location of the true fibre connections. Nstr counts how many such streamlines run from the predefined seed region to the predefined target region (Behrens et al. 2003). Nstr is an estimation of the number of the real fibres based on the artificial reconstruction of these fibres. It should be kept in mind that Nstr (represented by a parameter called ‘waytotal’ in FSL) is not a straightforward measure of tract integrity. It has been suggested that normalized values of waytotal should be used to avoid a possible tractability bias caused by subject motion or scanner noise. FA is a scalar measure of anisotropy. It is thought to reflect fibre density, axonal diameter and myelination in the white matter (Basser & Pierpaoli 1996). To avoid subjective thresholding, a probability-weighted average FA was calculated for each pathway and subject using the following equation (derived from: Hua et al. 2008):

$$\text{Mean FA} = \sum(\text{Pr}_i * \text{FA}_i) / \sum \text{Pr}_i \quad 1$$

Where Pr_i is the probability of the i th voxel to be part of the reconstructed tract, empirically decided by the number of streamlines that pass through the i th voxel divided by the total number of streamlines.

To assess the structural laterality of each connection, lateralization indices (LI) were calculated for both Nstr and FA using the following equation:

$$LI = (Left - Right) / (Left + Right) \quad 2$$

To see whether the absolute difference between left and right connections may also influence the behavioural measures, an absolute lateralization index (LA) was also calculated using the following equation:

$$LA = Left - Right \quad 3$$

Thus for both LI and LA, a more positive value indicates ‘more left-lateralized’ and a more negative value means ‘more right-lateralized’.

Regression analysis on the relationship between behavioural measures and structural connectivity profiles

Stepwise regression analysis implemented in SPSS 16.0 (*SPSS, Inc., Chicago IL*) was used to investigate whether each of these behavioural measures can be explained by the connectivity profiles of certain pathways. Behavioural measures were regressed on Nstr, LI of Nstr (LI_Nstr), LA of Nstr (LA_Nstr) and the summation of left and right Nstr (Sum_Nstr). Sum_Nstr was included as a regressor to control for brain size and the bias of tractability caused by subject motion and scanner noise. The gender of the subject (*gender*) and the sample to which the subject belongs (*sample*) were entered as control regressors as well.

The same stepwise regression analyses were carried out to investigate the relationship between the behavioural measures and FA.

Results

PCA analysis of the behavioural measures

The first three Principal Components (PCs) accounted for 67% of the variance. The first PC (PC1) explains 32.6% of the variance. The second PC (PC2) explains 19.4% and the third (PC3) 15% of the variance. The corresponding loadings are shown in Table 4.1. PC1 has positive loadings on all 7 behavioural measures. PC2 had positive loadings on *vocabulary learning*, *sound-symbol correspondence*, *IQ* (the largest loading) and *spatial working memory*, and negative loadings on *sound recognition*, *verbal working memory* and *grammatical inferencing*. PC3 had positive loadings on *IQ* and *spatial working memory* and negative loadings on *vocabulary learning*, *sound recognition*, *sound-symbol correspondence*, *grammatical inferencing* and *verbal working memory*.

Table 4.1 Loadings of the behavioural measures on the principle components

	Component		
	1	2	3
<i>Vocabulary learning</i>	.657	.214	-.273
<i>Sound recognition</i>	.438	-.712	-.108
<i>Sound-symbol correspondence</i>	.618	.386	-.111
<i>Grammatical inferencing</i>	.832	-.094	-.328
<i>IQ</i>	.341	.667	.119
<i>Spatial working memory</i>	.349	.116	.816
<i>Verbal working memory</i>	.587	-.436	.413

Language pathways

DTI fibre tractography discovered robust structural connections for all seed-target pairs in 97% of the participants (as in Figure 3.1, Chapter3). While connections between the parietal/posterior temporal lobe and BA6/BA44 are observed to mainly lie in the dorsal part of the brain, connections between the two

lobes and BA47 go through the ventral part. Connections between the two lobes and BA45 are seen in both dorsal and ventral parts of the brain. Inter-hemispheric pathways were shown in Figure 4.1. All of these pathways go through the corpus callosum.

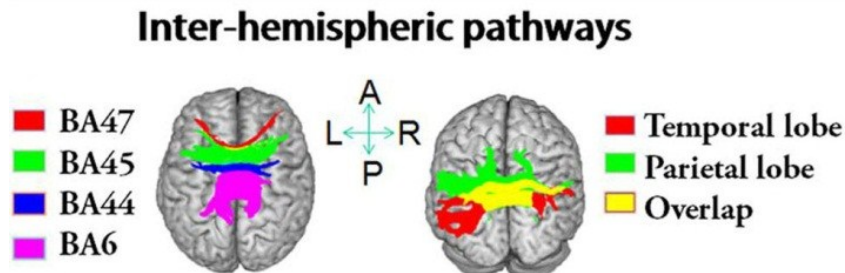


Figure 4.1 Inter-hemispheric pathways of BA6, BA44, BA45, BA47, parietal lobe and posterior temporal lobe projected on the MRICRON brain template. L: left hemisphere; R: right hemisphere; A: anterior brain; P: posterior brain.

Relationship between behavioural measures and structural connectivity in the language pathways

The step-wise regression analyses found the most optimal models for *vocabulary learning* (for Nstr, adjusted $R^2 = 0.14$, $p = 0.03$), *sound recognition* (for Nstr, adjusted $R^2 = 0.37$, $p = 0.04$), *sound-symbol correspondence* (for FA, adjusted $R^2 = 0.25$, $p = 0.003$), *grammatical inferencing* (for Nstr, adjusted $R^2 = 0.36$, $p = 0.002$), *IQ* (for Nstr, adjusted $R^2 = 0.76$, $p < 0.0001$; for FA, adjusted $R^2 = 0.24$, $p = 0.005$), *spatial working memory* (for Nstr, adjusted $R^2 = 0.32$, $p = 0.002$; for FA, adjusted $R^2 = 0.23$, $p = 0.006$), *verbal working memory* (for Nstr, adjusted $R^2 = 0.34$, $p = 0.003$). Table 4.2 shows the details of the best predictors suggested by each of these models. It should be noted that the significance of the predictor of Nstr *LA47P* (*absolute lateralization index of BA47-parietal pathway*) for *vocabulary learning* did not survive a Bonferroni correction. We still report this result because it seems

to be very consistent with previous findings (see Discussion for more details). All the significances reported in the results are Bonferroni corrected unless otherwise specified.

Table 4.2 Results of regression analysis on the relationship between behavioural scores and structural connectivity

a. <i>Vocabulary learning</i>			b. <i>Sound recognition</i>			c. <i>Sound-symbol correspondence</i>			d. <i>Grammatical inferencing</i>		
<hr/>			<hr/>			<hr/>			<hr/>		
Nstr FA			Nstr FA			Nstr FA			Nstr FA		
<hr/>			<hr/>			<hr/>			<hr/>		
<i>LA47P</i>	-.41!* n.s		<i>Gender</i>	.46* .34!*		<i>Inter45</i>	n.s. .72**		<i>LI45T</i>	.51* n.s.	
									<i>Sum6T</i>	.51* n.s.	
									<hr/>	<hr/>	

e. <i>IQ</i>			f. <i>Spatial working memory</i>			g. <i>Verbal working memory</i>		
<hr/>			<hr/>			<hr/>		
Nstr FA			Nstr FA			Nstr FA		
<hr/>			<hr/>			<hr/>		
<i>Sample</i>	.68** .49*		<i>Inter6</i>	.56** n.s		<i>Sum47T</i>	-.48* n.s	
<i>LA44P</i>	-.56** n.s		<i>LI47P</i>	n.s. -.56*				
<i>Inter45</i>	-.32* n.s.							
<i>LA47P</i>	-.37* n.s							
<i>LI47p</i>	.38* n.s.							
<i>L47T</i>	n.s. -.44*							

*: Bonferroni corrected $p < 0.05$; **: Bonferroni corrected $p < 0.01$; !*: Bonferroni not corrected $p < 0.05$; n.s.: not significant; L: left; R: right; LI: lateralization index; LA: absolute difference between L and R; Inter: inter-hemisphere connectivity; Sum: summation of L and R; 6: BA6; 44: BA44; 45: BA45; 47: BA47; T: posterior temporal lobe; P: parietal lobe.

Figure 4.2 shows the correlations between the four language aptitude tests and their best predictors.

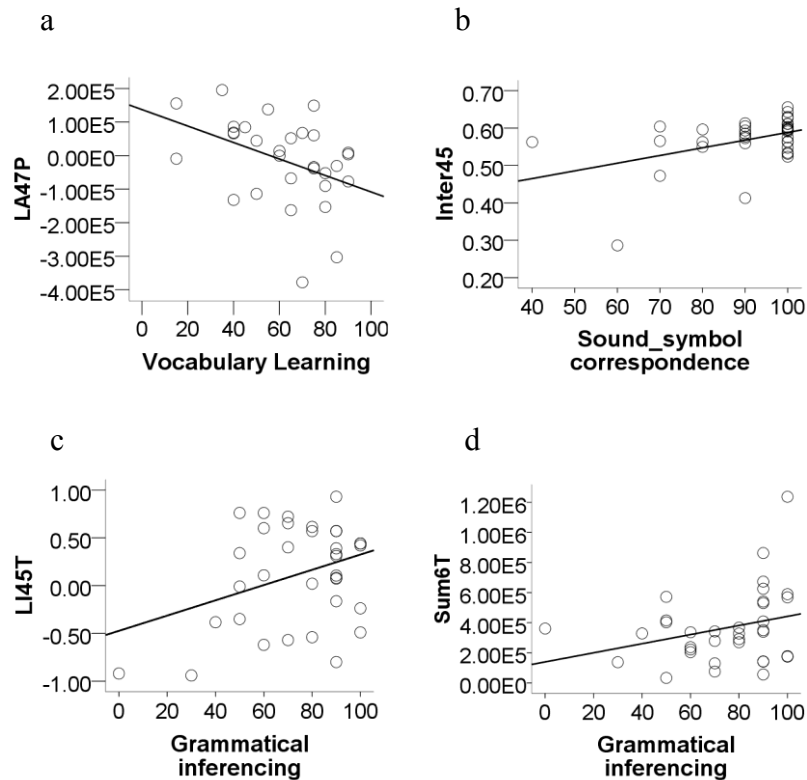


Figure 4.2 The correlation between a) the score of *vocabulary learning* test and the absolute lateralization index of Nstr (number of streamlines) of the BA47-Parietal pathway; b) the score of *sound-symbol correspondence* test and the FA of the inter-hemispheric BA45 pathway; c) the score of *grammatical inferencing* test and the lateralization index of FA of the BA45-Temporal pathway; d) the score of *grammatical inferencing* test and the summation of left and right Nstr of the BA6-Temporal pathway. LA: absolute lateralization index, i.e., absolute difference between the left and right pathway; LI: lateralization index; Inter: inter-hemispheric; Sum: summation of the left and right pathway; 6: BA6; 45: BA45; 47: BA47; T: posterior temporal lobe; P: parietal lobe.

Discussion

For the 7 behavioural measures, the first three Principal Components (PCs) explained most of the variance. PC1 was the largest component (32.6%) and represents the agreement between all these behavioural measures, suggesting that a general ability might be important to L2 acquisition. PC2 explains 19.4% and seems to suggest that *vocabulary learning*, *sound-symbol correspondence* and *spatial working memory* are more closely related to general *IQ* than *sound recognition* and

verbal working memory. Finally, PC3 explains 15% of the variance and distinguishes the tasks specifically designed to tap into language aptitude (*vocabulary learning, sound recognition, sound-symbol correspondence and grammatical inferencing*) from more generic measures (*IQ, spatial and verbal working memory*).

Vocabulary learning and BA47-parietal pathway

LA47P was suggested as the best predictor of *vocabulary learning*. Although this result did not survive Bonferroni correction, it seems to be in line with previous findings. The parietal lobe has been reported to be of great relevance for vocabulary knowledge (Mechelli et al. 2004; Price et al. 2007; Richardson & Price 2009); these structural imaging studies have consistently located an area in the parietal lobe (i.e., the supramarginal gyrus) that supports vocabulary learning. The grey matter density in this area was found to be positively correlated with vocabulary knowledge and was suggested to be ‘a neural marker for the number of words learnt’ (Richardson & Price 2009, p514). BA47 is known to be a semantic/lexical region as suggested by a comprehensive meta-analysis of language studies (Bookheimer (2002) and as proposed by the MUC model of language processing (Hagoort 2005a; Xiang et al. 2010). Overall, the present results seem to suggest that the communication between BA47 and the parietal lobe is very important in explaining the individual differences in *vocabulary learning*.

Sound recognition and gender

For *sound recognition*, *gender* was found to be the only significant predictor. T-test also revealed a significant gender difference on *sound recognition*. Previous

studies have shown that there is more variation in females than males when performing sound perception tasks, with performance in females being more affected by factors like voicing and context (Westerhausen et al. 2010; Yu 2010; Liederman et al. 2011). The larger variation on this task in females might lead to poorer performance in females compared to males. However, it should be noted that our sample contains more than twice of females (24) than males (11). Thus this result should be viewed with caution.

Sound-symbol correspondence and Inter-hemispheric BA45 pathway

The best predictor found for the language aptitude of *sound-symbol correspondence* was *Inter45*. The literature is rather sparse in this respect so we will try to present some hypotheses on the significance of this result. The *Sound-symbol correspondence* test requires participants to work out the relationship between the sounds and the writing system based on previously heard syllables and their transliterations in an unfamiliar alphabet. It might resemble the link between phonology and semantics (as represented by abstract symbols in this case). Besides its function for syntactical processing, BA45 has been found to be an overlapping area for both phonological and semantic processing (Poldrack et al. 1999; Bookheimer 2002; Xiang et al. 2010). This might tentatively suggest that BA45 could act as a possible neural link between phonology and semantics. The inter-hemispheric connectivity of BA45 thus could be a possible neural substrate for the *sound-symbol correspondence* task. Future studies are needed for further understanding of this result.

Grammatical inferencing and BA45-temporal and BA6-temporal pathways

The best predictors for *Grammatical inferencing* were LI45T and Sum6T. The function of BA45 for syntactic/grammatical processing has been well recognized (see for example: Bookheimer 2002; Musso et al. 2003). The functional connection between left BA45 and posterior temporal lobe has also been suggested to resemble the syntactic pathway in the perisylvian language network (Xiang et al. 2010). The present result consistently suggested that the lateralization of BA45-temporal pathway is important for *grammatical inferencing*.

Another predictor (*Sum_6T*, the summation of Nstr left and right BA6-temporal pathway) should be viewed with caution. The summation of Nstr was considered as a control regressor. It may be subject to influence of brain size (i.e., bigger brains may contain more fibres in total) and the subject motion or scanner noise (i.e., motion and noise may influence the total number of fibres which can be traced in the brain). Nevertheless, part of BA6 has been found to be responsible for the processing of hierarchical structures in artificial grammar learning (Friederici et al. 2008). In another study (Xiang et al. in preparation), we found that the lateralization of BA6-Temporal pathway changed with increasing L2 proficiency, while the summation of Nstr of both left and right BA6-Temporal pathway remained relatively constant. This suggests that the summation of Nstr of left and right BA6-Temporal pathway could be a possible indicator of the neural substrate responsible for components of the language aptitude.

IQ and sample, BA44-parietal, inter-hemispheric BA45, BA47-parietal, BA47-temporal pathways

Several significant predictors were found for *IQ*: *sample*, *LA44P*, *Inter45*, *LA47P*, *LI47P* and *L47T*. The neural substrate of *IQ* has been shown to involve a distributed network including the frontal lobe (BA44, 45, 47), temporal lobe and parietal lobe (Jung & Haier 2007; Shaw 2007; Deary et al. 2010). Previous DTI studies also revealed that *IQ* is correlated with the white matter integrity of both dorsal and ventral language pathways, such as the arcuate and uncinate fasciculi (Turken, Whitfield-Gabrieli et al. 2008; Thompson et al. 2009). Our results seem to be consistent with these findings. As for the factor of *sample*, it seems reasonable to be a predictor of *IQ* in this study because participants in Sample 1 were middle school graduates, while participants in Sample 2 were college/graduate students. The result of the t-test confirmed that participants in Sample 2 indeed had significantly higher IQs than those in Sample 1.

Spatial working memory and inter-hemispheric BA6, BA47-parietal pathways

For *spatial working memory*, *Inter6* and *LI47P* were found to be the best predictors. A recent meta-analysis (Bullmore et al. 2005) shows that *spatial working memory* tasks always involve BA6 and the Parietal lobe. The present results suggest that the inter-hemispheric connectivity of BA6 and the lateralization of Nstr BA47-parietal lobe are both important for *spatial working memory*, but it is not clear what the role of BA47 might be.

Verbal working memory and BA47-temporal pathway

For *verbal working memory*, *Sum47T* was found to be the best predictor. For the same reasons discussed for *Sum_Nstr*, this result should be viewed with caution. It should be mentioned that the present study used a different paradigm for testing the *verbal working memory* compared to many previous studies. We used sentence materials and asked participants to try to read and understand the sentence while remembering its last word. This paradigm may lead participants to rely on the meaning of the sentence to help remembering the final words. This could be the reason why the semantic pathway (BA47-Temporal) was found as a predictor for *verbal working memory* in the present results. Previous studies have most often used simpler stimuli such as consonants and letters, for which participants might mainly rely on a shallower processing of these stimuli, and these studies reported that BA6/44/45 and the dorsal phonological pathway were relevant for *verbal working memory* (D'Esposito et al. 1998; Smith & Jonides 1998; Catani et al. 2007).

Caveats and future directions

It can be noticed that the regression analyses of *Nstr* and *FA* did not suggest the same predictors. This might indicate that they probably do not measure the same properties of a pathway, a phenomenon that has been previously reported in DTI studies (Catani et al. 2007; Lebel & Beaulieu 2009).

It should be noted that the currently available methods for measuring the structural connectivity are subject to distortions due to factors like crossing fibres and limitations of the algorithms, which may result in a decreased statistical power of the present study. For example, measurement of *FA* in regions where there are crossing fibres are found vulnerable to noise and scanning parameters. The *SD*

(standard deviation) differences of FA were found to correspond to roughly 5–7% of the trace value in these regions, and much lower in other regions (0–2%) (Alexander et al. 2001).

As the first of its kind, the research reported here was exploratory and we are looking forward to more future replications.

Chapter 5

Genetic modulation of Broca's and Wernicke's area as structural hubs in the large-scale brain networks

This chapter is a slightly modified version of:

Xiang, HD, Nijhuis EHJ, Norris DG, Hagoort P. (in preparation). Genetic modulation of Broca's and Wernicke's area as structural hubs in the large-scale brain networks.

Abstract

We investigated the complex organization of the brain networks by employing advanced graph theoretical techniques, aiming to examine the network properties of the classical language areas. We discovered, that Broca's area and Wernicke's area are structural hubs in the complex brain networks. It suggests that Broca's and Wernicke's area play a central role in the communication within the structural language networks. We further investigated the effects of the CNTNAP2 genotype variations on the network properties of the Broca's and Wernicke's hubs. We found that the graph topology of the Wernicke's hub was affected by the CNTNAP2 genotype. It suggests that the influence of genetic factors to human language function can be detected in the topology of complex brain networks. To the best of our knowledge, this is the first time that a genetic influence on the complex organization of the brain networks is reported.

Introduction

Recent studies have shown that human language processing employs brain networks involving multiple areas (Price 2010; Hagoort 2005a). It is thus relevant to study brain language function from a networks perspective. Among those areas that are involved in the language networks, Broca's area and Wernicke's area are no doubt the most well-known ones. However, a direct and clear answer is still missing to why these two areas are so important for language functions. Is it because in themselves they support central aspects of language processing? Or is it because they play a crucial role in the communication of the brain language networks, acting like structural cores or hubs?

The present study aims to answer the second questions by investigating the roles of Broca's and Wernicke's area in the complex organization of the brain language networks. For this purpose, advanced graph theoretical techniques were employed.

Graph theory is a popular mathematical tool for representing complex data sets composed of related entities (Watts, 2004). In graph theory, a graph is a collection of dots that may or may not be connected to each other by lines. A "dot" is called a **node**. A "line" is called an **edge**. The graph theory has been applied to studies of many natural and man-made networks such as metabolic pathways, genomics, and the structure of the World Wide Web. It has recently been adopted by cognitive neuroscientists for studying brain networks (Bullmore & Sporns, 2009). Analyses of large-scale structural brain networks can reveal structural cores (or hubs) that link all major structural modules (Hagmann et al. 2008). In the present study, we are particularly interested to see if the classical Broca's and Wernicke's area will show up as structural hubs.

Furthermore, inspired by the results of a previous study in our group (Snijders et al. submitted), we looked into the effects of the CNTNAP2 (contactin-associated protein-like 2) genotype on the graphical network properties of these two areas.

CNTNAP2 is down-regulated by another well-established language-related gene - FOXP2 (Vernes et al. 2008). Several studies have linked CNTNAP2 to language abilities (Alarcon et al. 2008; O'Roak et al. 2011; Poot et al. 2010; Strauss et al. 2006; Vernes, et al. 2008; Whitehouse, Bishop, Ang, Pennell, & Fisher, 2011). The previous study by our group has discovered that the variation in genotype (A>T) of a common single nucleotide polymorphism, (SNP) rs7794745, of CNTNAP2 affects the functional connectivity between the posterior inferior frontal region and Wernicke's area (Snijders et al. submitted). The present study investigated whether this CNTNAP2 SNP may also have effects on the network properties of the two classical areas in the large-scale structural brain networks.

Methods

Participants

Our participants include 42 genotyped European Caucasian volunteers (14 males) in the high-quality DICOD-1 (Donders Institute Connectivity Database -1) developed at the Donders Institute for Brain, Cognition and Behaviour. They are all right-handed, healthy adults between the age of 19-29 years. All participants gave written informed consent and the study was conducted according to institutional guidelines of the local ethics committee (CMO protocol region Arnhem-Nijmegen, The Netherlands).

DNA-isolation and genotyping of all participants were carried out in a CCKL-accredited laboratory at the Department of Human Genetics of the Radboud

University Nijmegen Medical Centre.

Data acquisition

All participants were scanned on a Siemens 3T TIM Trio system with a 32 channel head coil at the Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen.

High resolution anatomical scans were acquired using a T1-weighted 3D MPRAGE sequence with TE=3.03ms, TR=2300ms, TI=1100ms, a flip angle of 8 ° with 1mm isotropic voxels.

We used Diffusion Tensor Imaging (DTI) to investigate the structural connectivity of the brain, to provide the measurement of structural connections for the graph theoretical analysis of the structural brain networks. DTI produces images of biological tissues weighted with the local micro-structural characteristics of water diffusion, and is capable of tracing structural connections between brain regions in vivo and providing quantitative measures of brain white matter organization (Le Bihan et al. 2001). Diffusion weighted imaging volumes were acquired using a single-shot echo-planar imaging (EPI) sequence with phase encoding in the anterior to posterior direction, with TE=101 ms, TR=13.0s, 2mm isotropic voxels and taken in 256 non-collinear directions at a b-value of 1500 s/mm². In addition, 28 volumes were acquired with b=0 s/mm².

Graph theoretical Analysis

For each of the 42 subjects, twenty different connectomes have been generated for which several network measures were estimated. A detailed description of the processing steps is given in the following sections, which

resemble the ones described in (Nijhuis2011 et al. submitted).

Step 1: Creation of Neocortical Network Nodes

Previous work has used fixed anatomical based templates across a population of subjects (Gong et al. 2009; Hagmann, et al. 2008). This approach benefits from being able to compare anatomically identical nodes across subjects. Other studies have argued that defining nodal configuration with anatomical templates may lead to inappropriate node representations, which might lead to incorrect functional network estimates or to poorly characterizing U-fibres (the 'U' shape short association fibres) (Smith et al. 2011; Zalesky et al. 2010). We therefore resolved this dilemma using a template free approach and individually parcellated each of our 45 subjects multiple times, in order to reduce the effects of node selection biases and potential fragmentation of hubs.

The anatomical scans were analysed using Freesurfer (Dale, Fischl, & Sereno, 1999) to segment the brains into cortical and subcortical structures. Each neocortical hemisphere was parcellated twenty times into 500 ROIs (regions of interest) using the k-means algorithm (Seber 1984) on the Euclidean distances between grey matter voxels. The k-means clustering partitions anatomical brain voxels into clusters in which each voxel belongs to the cluster with the nearest mean. The procedure is not deterministic as the final parcellation depends on the random initialization of the k-means. The process therefore produced twenty different neocortical parcellation schemes for each brain. The contiguous ROIs had an average size of $0.1\% \pm 0.017\%$ (SD, standard deviation) of the total neocortical volume. Each of the ROIs was then used as node in the structural connectivity mapping step.

Step 2: Diffusion Preprocessing and Tractography.

The diffusion-weighted images were checked for motion, cardiac and table

vibration-induced artefacts using the PATCH algorithm (Zwiers, 2010). The volumes were realigned and corrected for eddy current-induced distortions using the integrated approach described in (Andersson & Skare, 2002). Finally the volumes were unwarped in the phase encoding direction onto the anatomical scan to reduce the effects of phase evolution in the EPI read out direction (Visser et al. 2010). We used the multi-fibre reconstruction PASMRI with 16 basis functions (Cook 2006) and performed interpolated deterministic tractography with a 0.2mm stepping size (Behrens et al. 2003), using the coregistered Freesurfer white matter mask with 1mm isotropic voxels for seeding in a maximum of three main principal diffusion directions. The choice of the reconstruction and tractography methods was driven by results presented in (Guevara et al. 2011), who showed that using a spherical deconvolution transform reconstruction in combination with deterministic tractography, results in the highest fraction of valid fibre tracts found in a phantom.

Step 3: Structural Connectivity Mapping

For each brain a network was reconstructed by defining the ROIs as nodes and the number of tracked fibres between ROIs as the edge strength. Next, the network matrices were binarized without thresholding the strength of a connection. The resulting connectivity matrices were used for further analysis.

Step 4: Connectome Analysis.

A network analysis was performed using the Brain Connectivity Toolbox (<http://www.brain-connectivity-toolbox.net>) to determine the node degree and betweenness centrality for all twenty segmentations of each brain. The results were mapped back on the cortical surfaces to produce subject specific hub maps. Note, in this step, each subject specific hub map still contains the twenty segmentations.

Step 5: Mapping Network Parameters to Average surface.

In the last steps we registered all subject specific maps to the Freesurfer average surface, where they were smoothed with a 10 mm FWHM kernel and finally averaged (on subjects) and rescaled to a maximum value of 100. The final outcomes of the analysis are displayed in Figure 5.1.

Step 6: Broca's and Wernicke's Hub area selection

Hubs were identified on the basis of the group average hub map where the node centrality was higher than 50, when the maximum value is rescaled to 100. Node Centrality of a node measures how many of the shortest paths between all other node pairs in the network pass through it. A node with high centrality is thus crucial to efficient communication (Bullmore & Sporns 2009). This procedure determined several distinct anatomical areas as hubs, among which Broca's area and Wernicke's area were clearly seen. ROIs were then hand-drawn around the Broca's and Wernicke's hubs on the inflated average surface to include those voxels that have a higher Node Centrality than 0.5. Next, the maximum of the individual map (warped on the average surface) was calculated for the given ROI. Besides Node Centrality, Node degree was also calculated for each of the ROIs. Node Degree is the number of connections that link a node to the rest of the network. It is the most fundamental network measure (Bullmore & Sporns, 2009).

Comparisons of the CNTNAP2 SNP on the Broca's and Wernicke's hubs

The Multivariate Analysis of the General Linear Model (GLM) implemented in SPSS 18 (*SPSS, Inc., Chicago IL*) was employed to compare the properties of these two hubs between the two CNTNAP2 gene groups. For genotype grouping, carriers of at least one T allele were grouped together and compared to carriers of the AA homozygous genotype. The comparisons were based on the maximum of the Node

Degree or Node Centrality of these two hubs of each subject.

Results

The Graph theoretical analysis obtained a comprehensive structural connectivity map of the brain, as shown in Figure 5.1.

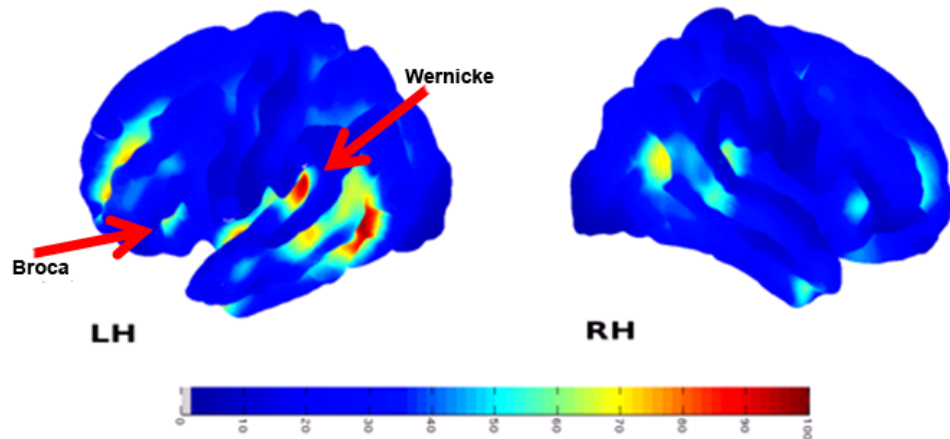


Figure 5.1 Structural hubs as revealed by the graph theoretical analysis. The color represents the value of the Node Centrality of the voxels. The red arrows point to the Broca's hub and Wernicke's hub.

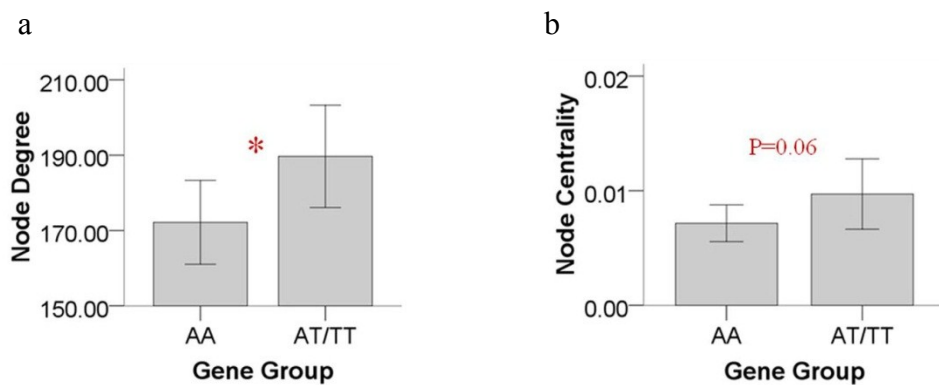


Figure 5.2 The difference between the AA and AT/TT gene groups on the Node Degree (a) and Node Centrality (b) for the Wernicke's hub. *: $p < 0.05$, Bonferroni corrected; $p=0.06$ is also Bonferroni corrected.

It identified several distinct anatomical areas as hubs, such as bilaterally, the dorsal lateral prefrontal cortex, temporal pole, posterior temporal lobe

parietal-occipital sulcus, anterior superior temporal lobe and the right precuneus (Nijhuis2011 et al. submitted). Most interestingly, the two classical language areas, i.e., Broca's area and Wernicke's area were revealed as hubs (Figure 5.1). Moreover, these hubs were clearly left lateralized.

Genotyping of the participants identified 20 T-allele (AT/TT) carriers and the other 22 participants with the AA homozygous genotype. Based on the results of previous studies (Snijders et al. submitted), we put the T-allele carriers into one gene variation group and the AA carriers into the other gene variation group. Comparisons between our gene groups revealed a significant difference on the maximum of Node Degree of the Wernicke's hub (AT/TT > AA; $p < 0.05$, Bonferroni corrected; Fig 2a). The maximum of Node Centrality of the Wernicke's hub also showed such a near significant difference between our two gene groups (AT/TT > AA; $p = 0.06$, Bonferroni corrected; Fig 2b). The Broca's hub did not show any difference between our two gene groups. The results of the GLM model also suggested that there are significant gender differences on Node Degree (males > females) of the Broca's hub and Node Centrality (females > males) of the Wernicke's hub (uncorrected $p < 0.01$ for both).

Discussion

We performed the first graph theoretical study that focused on the language networks. The classical Broca's area and Wernicke's area were clearly and directly shown as structural hubs in the complex brain networks. It suggests that Broca's and Wernicke's area play a central role in the communication of language-relevant areas in the brain. This might be one of the reasons why they are so important for language functions. Most of the other hubs we obtained from the graph theoretical

analysis are generally consistent with previous findings. For example, the precuneus, posterior cingulate cortex and dorsal lateral prefrontal cortex have been suggested as hubs in other graph theoretical studies (Hagmann, et al. 2008). The temporal pole has been suggested by many language studies to be a semantic hub for language processing (Patterson, Nestor, & Rogers, 2007).

An additional interesting result is that both measurements (Node Degree and Node Centrality) suggested a significant (or near significant) difference between our two CNTNAP2 gene groups on the properties of the Wernicke's hub. Previous studies have revealed that CNTNAP2 is a cell-adhesion molecule expressed during development. It was suggested to be involved at the level of the synapse (Alarcon, et al. 2008; Zweier et al. 2009). It contributes to the shaping of the properties of neural networks by specifying synaptic functions (Sudhof 2008). This makes CNTNAP2 a possible candidate which regulates the properties of complex neural networks.

Furthermore, the location of the Wernicke's hub almost exactly overlaps with the area that was found to show a CNTNAP2-genotype-specific effect during sentence vs. word processing (Snijders et al. submitted). This brain area was found to show a stronger activation (sentences > words) for the AT/TT genotype than for the AA genotype group. It is interesting to note, that this area is the only region that showed more effective connectivity to the posterior inferior frontal lobe for the AA group than for the AT/TT group in the effective connectivity analysis for sentence ambiguous compared to sentence unambiguous conditions. Rather than the traditionally arbitrarily assigned function for language comprehension, Wernicke's area has been found to play a role in merging different sources of information into a

common conceptual memory representation (Willems et al. 2009). Based on their own results and previous findings, Snijders et al. (submitted) have suggested that the AT/TT participants seem to be more lexically-driven in their language-processing styles. The AT/TT participants use this Wernicke's area more than the AA participants, and they depend less on the interplay between left inferior frontal and posterior temporal regions during word and sentence processing. It implicates that the functional role of this Wernicke's hub in the language networks is more important for the AT/TT participants than for the AA participants, for this functional role is more shared with the left inferior frontal lobe for the latter than for the former. This functional account seems to be consistent with our findings. In our results, the AT/TT gene group showed higher Node Degree and Node Centrality for the Wernicke's hub than the AA group. A higher Node Degree for the AT/TT group means that Wernicke's area of this group is connected with more brain regions anatomically, which suggests Wernicke's area of the AT/TT group may be able to communicate with more brain areas than the AA group. A higher Node Centrality for the AT/TT group means that Wernicke's area of this group is the centre of the shortest path for more brain structural pathways, which suggests that in their case Wernicke's area plays a more important connector role than for the AA group.

In our results, the Broca's hub did not show a significant difference between the two CNTNAP2 genotypes. This result seems to be in line with the previous finding (Snijders et al. submitted). Snijders et al. found that it was the posterior inferior frontal lobe but not the classical Broca's area (BA44, 45) that showed a CNTNAP2-genotype-specific language processing effect.

We found that the Broca's hub showed a significant gender difference on Node

Degree (males > females). The Wernicke's hub also showed an opposite gender difference on Node Centrality (females > males). The gender of the participants was taken as a covariate in our analysis. Thus we do not want to draw further conclusions about these results. However, it has been reported that males and females differ significantly on some properties of the large-scale structural brain networks (Gong, et al. 2009; Yan et al. 2011).

Finally, the present study provides a new way for studying the genetic effects on the properties of large-scale brain networks. We narrowed down the statistical analysis to a limited number of hubs in the networks based on prior knowledge. This avoids the overwhelming multi-comparison problem that exists in many current gene and brain network studies.

Conclusion

Our graph theoretical analysis discovered that Broca's area and Wernicke's area are structural hubs in the complex brain networks. It suggests that Broca's and Wernicke's area play a central role in the communication within the structural language networks. We further revealed that the graph topology of the Wernicke's hub was affected by the CNTNAP2 genotype. It suggests that the influence of genetic factors to human language function can be detected in the topology of complex brain networks. To the best of our knowledge, this is the first time that a genetic influence on the complex organization of the brain networks is reported.

Chapter 6

Summary and discussion

Summary

This thesis studied the brain function for language at the network level. We investigated the functional and structural organization of the brain networks, and their connectivity pattern and relation to language learning, capacity and language-related genetics.

In Chapter 2, we used fcMRI to infer the functional organization of Broca's complex and the perisylvian language networks by investigating their functional correlations. A clear topographical functional connectivity pattern in the left middle frontal, parietal and temporal areas was revealed when seeding from the three subregions (pars opercularis, pars triangularis and pars orbitalis) of Broca's complex. The results are consistent with previous studies on the language function of brain. They support the assumption of an anterior-ventral to posterior-dorsal functional gradient in Broca's complex that corresponds to the functional division for phonology, syntax and semantics, as proposed by the MUC model. It indicated a topographical functional organization and division of labour for phonological, syntactic and semantic function in the left frontal, parietal and temporal areas.

In Chapter 3, we used DTI to investigate whether the achieved L2 proficiency during L2 acquisition could be explained by the reorganization of structural connectivity between core language areas. We found that, with increasing L2 proficiency, the hemispheric dominance of the BA6-Temporal pathway (mainly along the arcuate fasciculus) shifts from the left to the right hemisphere in the initial learning stage. With increased proficiency, however, the dominance is again found in the left BA6-Temporal pathway. This result is in accordance with similar findings in behavioural and functional neuroimaging studies on L2 acquisition. This is the first time that a L2-proficiency-dependent laterality shift in structural connectivity

of language pathways during L2 acquisition has been observed. It suggests that structural connectivity in (at least part of) the perisylvian language network may be subject to fast dynamic changes following language learning.

In Chapter 4, we studied the relationship between the language aptitude and the structural connectivity of language pathways in the adult brain. We measured four components of language aptitude (*vocabulary learning*; *sound recognition*; *sound-symbol correspondence*; and *grammatical inferencing*) using the LLAMA language aptitude test (Meara, 2005). Regression analysis suggested significant correlations between most of these behavioural measures and the structural connectivity of certain language pathways, i.e., *vocabulary learning* and the BA47-Parietal pathway, *sound-symbol correspondence* and the inter-hemispheric BA45 pathway, and *grammatical inferencing* and the BA45-Temporal pathway and BA6-Temporal pathway. This is the first study that looked into the relationship between language talents and the connectivity of the structural brain networks. These results are generally in line with other relevant findings in the literature.

In Chapter 5, we investigated the complex organization of the brain language networks by employing the graph theoretical techniques. We discovered, for the first time, that the classical Broca's area and Wernicke's area are structural hubs in the large-scale brain networks. It suggests that Broca's and Wernicke's area play a central role in the communication of the structural language networks. We further investigated the effects of the CNTNAP2 genotype on properties of the Broca's and Wernicke's hub. We found that the graph topology of the Wernicke's hub was affected by the CNTNAP2 genotype. It suggests, for the first time, that the influence of genetic factors to human language function can be detected in the topology of the complex brain networks.

Discussion

The laterality of the language networks

One important contribution of this thesis is that we revealed the lateralization of the brain language function at the network level. In Chapter 2, we used fcMRI to investigate the functional organization of the perisylvian language networks by seeding from the three subregions (pars opercularis, pars triangularis and pars orbitalis) of Broca's complex and their right hemisphere homologues. A topographical functional connectivity pattern is only observed in the left hemisphere for the right-handed subjects. The left lateralized topographical connectivity pattern probably suggests that the left hemisphere layout follows a more functionally parcellated segregation of language function than the right hemisphere. It indicates that the left hemisphere may become more specialized for the language function than the right hemisphere in evolution. In Chapter 5, the graph theoretical analysis on the large-scale language networks identified several language-related hubs, such as Broca's area, Wernicke's area, temporal pole, posterior temporal lobe, and anterior superior temporal lobe. These hubs clearly show a left lateralized dominance on the hub map for the right handers. To summarize, both results give direct evidence to a both functionally and structurally lateralized language network in the brain.

The plasticity of the language networks

We now know that the human brain is a highly plastic organ throughout the life span (see reviews: Buonomano & Merzenich 1998; Johansson 2004; Pascual-Leone et al. 2005; Boyke et al. 2008; Draganski & May 2008). Fast dynamic changes in structural connectivity in the brain have been found for working memory and action

(Johansen-Berg et al. 2010, review). However, it is the first time that a dynamic plasticity on structural connectivity of the language networks is revealed. This thesis found a L2-proficiency-dependent laterality shift in the structural connectivity of the language pathways during L2 acquisition. It suggests a plastic structural connectivity in the perisylvian language network that may be subject to fast dynamic changes following mental activities such as language learning. It also implies that lateralization of the language pathways, or maybe even other structural pathways, may shift back and forth depending on an individual's current mental state. I am looking forward to future studies with larger samples and improved imaging and analysis techniques to replicate and further investigate this kind of fast dynamic structural connectivity changes in the brain networks.

The genetic influence on the language networks

The psychophysiological or genetic factors that predetermine the human language talents are hot topics in the research field. In this thesis, Chapter 4 and 5 made a contribution to this research. We found that the performances of most of the language aptitude tests are related to the structural connectivity of certain language pathways, such as *vocabulary learning* and the BA47-Parietal pathway, *sound-symbol correspondence* and the inter-hemispheric BA45 pathway, and *grammatical inferencing* and the BA45-Temporal pathway and BA6-Temporal pathway. These results are generally in line with other relevant findings of functional-neuroimaging studies in the literature. They seem to suggest that (at least some of) the psychophysiological factors may predetermine the human language talents. We also found that the properties of the Wernicke's hub as a structural core in the complex brain networks are influenced by the CNTNAP2 genotype. The

Wernicke's hub revealed a higher Node Degree and Node Centrality for one gene group than for the other. It seems to indicate that the psychophysiological factors (such as the hub properties in this case) might be influenced by the genetic factors. To summarize, the two emerged results seem to suggest that there are genetic factors that may influence the psychophysiological traits of the language networks of the brain, and in turn it might be able to predict (at least some aspects of) the language function of human individuals.

From the language networks to the language-readiness – the overarching perspective

In recent decades, neuroimaging studies on the neural infrastructure of language are usually (or mostly) conducted with certain on-line language processing tasks (Bookheimer 2002 review). These functional neuroimaging studies helped to localize the language areas in the brain and to investigate the brain activity during explicit language processing. However, little is known about what is going on with the language areas when the brain is 'at rest', i.e., when there is no explicit language processing running. Taking advantage of the fMRI and DTI techniques, this thesis is able to investigate the language function 'off-line' at the neuronal network level and the connectivity among language areas in the brain. It revealed an informative image of the functional and structural organization of the brain networks. These networks seem to be optimized for the human language function even when there is no explicit language processing running.

Based on patient studies, the traditional, classical model on the perisylvian language network specifies a "Broca's area – Arcuate Fasciculus – Wernicke's area" loop (Ojemann 1991). With the help of modern neuroimaging techniques,

researchers have been able to track language pathways that involve more brain structures than are in the classical model, and relate them to certain language functions (Friederici 2009, review). In such a background, a large part of this thesis made a contribution to the study of the topology of the language networks. To the best of our knowledge, this thesis might be the first one to study the topology of the language networks by employing these advanced neuroimaging techniques. It revealed that the language networks form a topographical functional connectivity pattern in the left hemisphere for the right-handers. This functional connectivity pattern seems to be organized with a division of labour for phonology, syntax and semantics, as suggested in the MUC model that is based on previous functional neuroimaging studies (Hagoort 2005, see more details in Chapter 2). This thesis also revealed the importance of structural hubs, such as Broca's and Wernicke's areas, which have more connectivity to other brain areas and play a central role in the language networks. It provides a possible explanation for the importance of the classical Broca's and Wernicke's area for the language function. Furthermore, as discussed in the beginning of the Discussion, this thesis revealed both functionally and structurally lateralized language networks in the brain. It resonates with the left-lateralized activation patterns that are found for most language-processing tasks in functional neuroimaging studies (Lurito & Dziedzic 2001).

The consistency between what is found in this thesis and what has been known from previous functional studies seems to suggest, that the human brain is optimized and 'ready' for the language function even when there is currently no explicit language-processing running. In the research of language evolution, the biological pre-adaptations for the modern language system are referred to as 'the language-readiness' of the human brain (Hurford & James 2003). Chomsky has

claimed that language is a biological phenomenon. He believes that the language template, with pre-existing fine organization, is pre-organized in the neuronal structure of the brain (Chomsky 1959). This kind of view falls into the so called “Nativism model” (Cook & Newson, 1996). This thesis discovered that the structural connectivity of certain language pathways or language hubs seems to have meaningful relationships with language aptitude or genetic factors. It implies that (at least part of) the organization of the language networks in the brain may biologically pre-exist. In summation, the results of this thesis seem to support the Chomsky (or Nativism) view of the language-readiness of the human brain.

However, this thesis also detected that the laterality of the structural connectivity of some language pathways might be subject to fast dynamic changes following short-term language learning. This result suggests a dynamic interaction between the structural networks of the brain and the external environment. In this sense it seems to favour another model, the so called ‘constructivist model’, which assumes that the language system is built up constantly from a continuous interaction with a well-structured environment (Piaget 1980). As mentioned before, the human brain has been found to be a highly plastic organ throughout the life span (see reviews: Boyke et al. 2008; Draganski & May 2008). It is possible that (at least) some parts of the observed brain networks that showed the language-readiness, are formed by the interaction between the brain and the environment.

To conclude, a ‘language-ready’ brain of the human being could be made possible both by having a biologically pre-existing ‘language-template’ and by interacting with the environment. We suggest that future studies on this topic should focus more on what are the pre-existing features of the ‘language-ready’ human

brain, and what features (and to which extend it) can be shaped by the environmental interactions, rather than continue to debate on a 'all or none' answer.

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References

Appendices

Supplementary Material for Chapter 3

Cloze test

Instructions Dutch proficiency test

This test consists of a story, in which the second half of every other word has been left blank. Your task will be to complete the incomplete words in such a way, that a meaningful story is created.

The partly omitted words should be completed with the same amount of letters or one more letter than the number of letters that is already printed. So if the sentence is

“Hij heeft een bo__”, it is for example correct to complete this word as ‘boek’, but incorrect to complete it as ‘bom’ (too short) or ‘boodschap’ (too long). It would also be correct to complete the word by adding three more letters.

NB. In this test, the letter ‘ij’ is counted as one letter (but oe, eu, ui, etc. are counted as two letters).

Importantly, the context of the story should always be taken into account when you are completing the words.

The story consists of three parts, and continuously increases in difficulty. Do not worry if you cannot complete many words, as the test is rather difficult. If you do not know a word, you may skip it. The test has to be finished within 20 minutes. If you cannot complete 10 words in a row, you may quit as well.

If you have any questions, please do not hesitate to ask them!

Good luck!

DE TAALCURSUS

De cursus is in een oude school. De school ligt aan een drukke straat.
De str_____ is mid_____ in d_____ stad. J_____ kunt hi_____ gemakkelijk
ko_____
met d_____ bus. M_____ kan e_____ niet go_____ parkeren. La_____ de au_____ dus
ma_____ thuis.
B_____ de sch_____ zijn win_____. Bijna al_____ winkels z_____ niet
gr_____,
maar w_____ druk.

Vroeger werd het gebouw gebruikt door een technische school. Dat kun
je op sommige plaatsen nog goed zien. Er is bijvoo_____ een
lok_____ waarin mach_____ gestaan heb_____. De ga_____ in d_____
vloer z_____ nog ste_____ niet di_____ gemaakt.
H_____ lokaal i_____ ook ve_____ groter d_____ de and_____ lokalen.
Tus_____ de mid_____ kunnen som_____ cursisten hi_____ nu h_____
brood ope_____ .

Ieder jaar zegt het gemeentebestuur tegen de cursusleiding dat in het
komende jaar een grote onderhoudsbeurt wordt uitgevoerd. Bovendien
mo_____ de verwarmings_____ worden verv_____,
want regel_____ zitten al_____ cursisten 's win_____ in
di_____ kleren.
O_____ in d_____ opzicht la_____ de geme_____ de curs_____ aan
h_____ lot ov_____. De cursus_____ denkt d_____ de
bezuin_____ weer ro_____ in h_____ eten zul_____ gooien.

Samenvatting

Translated by Joost Wegman& Monique Diks based on the original English
sumarry and discussion.

Dit proefschrift onderzoekt taalfuncties in het brein op het niveau van samenwerkende netwerken. We hebben hiervoor de functionele en structurele organisatie van breinnetwerken en hun connectiviteitspatronen en relaties met het leren van taal, taalvermogen en taalgerelateerde genen onderzocht.

Om dit te onderzoeken hebben we in hoofdstuk 2 met behulp van fMRI (functional connectivity Magnetic Resonance Imaging) de functionele organisatie van het complex van Broca en van het perisylvische taalnetwerk af proberen te leiden door hun functionele correlaties te onderzoeken. De resultaten wijzen op een topografische functionele organisatie en taakverdeling voor fonologische, syntactische en semantische functies in de linker frontale, pariëtale en temporale hersengebieden.

In hoofdstuk 3 hebben we met behulp van DTI (Diffusion Tensor Imaging) onderzocht of de bereikte vaardigheid in een geleerde tweede taal (L2) verklaard kon worden door een reorganisatie van de structurele connectiviteit tussen de centrale taalgebieden. We ontdekten dat met toenemende vaardigheid in L2 de dominantie van de BA6-temporale vezelverbindingen (voornamelijk langs de arcuate fasciculus) na de eerste leerfase van de linker- naar de rechterhersen helft verschuift. Met toenemende taalvaardigheid in L2 verplaatst de dominantie echter weer terug naar het linker BA6-temporale netwerk. Dit suggereert dat de structurele connectiviteit in (ten minste een deel van) het perisylvische taalnetwerk snelle dynamische veranderingen ondergaat als gevolg van het leren van taal.

In hoofdstuk 4 onderzochten we het verband tussen taalvaardigheid en de structurele connectiviteit van taalnetwerken in het volwassen brein. We hebben vier aspecten van taalvaardigheid gemeten (woordenschat, geluidherkenning, klank-tekencorrespondentie en grammaticale deductie) met de LLAMA-

taalvaardigheidstest (Meara, 2005). Regressieanalyse duidt op significante correlaties tussen de meeste van deze gedragsmaten en de structurele connectiviteit van bepaalde taalnetwerken. Deze resultaten zijn grotendeels in overeenstemming met andere relevante bevindingen in de literatuur.

In hoofdstuk 5 onderzochten we de complexe organisatie van taalnetwerken in het brein door middel van grafentheorie. We ontdekten dat de klassieke gebieden van Broca en Wernicke belangrijke verbindingscentra zijn in het netwerk van het gehele brein. Bovendien onderzochten we de effecten van het CNTNAP2-genotype op de eigenschappen van deze verbindingscentra van Broca en Wernicke. We toonden aan dat de graaftopologie van Wernicke's centrum beïnvloed werd door het CNTNAP2-genotype. Dit doet voor het eerst vermoeden dat de invloed van genetische factoren op menselijke taalfunctie waargenomen kan worden in de topologie van de complexe taalnetwerken.

Samenvattend kunnen we zeggen dat, door gebruik te maken van geavanceerde neuro-imagingtechnieken, dit proefschrift in staat is om de taalfunctie 'offline' te onderzoeken, dus op het moment dat er geen expliciete taalverwerking plaatsvindt. Het legt een informatief beeld bloot van de functionele en structurele organisatie van de breinnetwerken. De overeenstemming tussen de bevindingen in dit proefschrift en kennis uit eerdere functionele studies wijst erop dat het menselijke brein geoptimaliseerd en 'klaar' is voor taalfuncties, zelfs op momenten dat er geen expliciete taalprocessen plaatsvinden. Dit proefschrift toont aan dat de structurele connectiviteit van bepaalde taalnetwerken of taalcentra in het brein betekenisvolle relaties heeft met taalvaardigheid of genetische factoren. Het impliceert dat de organisatie van taalnetwerken in het brein (tenminste deels) mogelijk biologisch geprepareerd zijn. Dit proefschrift laat echter ook zien dat de mate waarin de

structurele connectiviteit van sommige taalnetwerken links- of rechtsdominant is onderworpen is aan snelle dynamische veranderingen die het gevolgd zijn van het leren van een taal op de korte termijn. Dit resultaat duidt op een dynamische interactie tussen de structurele netwerken van het brein en de externe omgeving. Concluderend kunnen we stellen dat het menselijk brein dat 'klaar is voor taal' mogelijk wordt gemaakt door zowel een biologisch geprepareerde 'taalmal' als door interacties met de omgeving.

中文概述

本论文通过对大脑语言网络的研究来研究人类的语言功能。我们考察了与语言学习、语言能力和语言可遗传性相关的大脑网络的功能和结构组织特点及其联结模式。

在第二章中，我们使用静息态功能核磁共振技术（fcMRI）研究了大布洛卡氏区和外侧裂周区语言网络的功能联结状况，并以此来考察该网络的功能组织结构。结果发现大脑左侧前额叶、后颞叶和顶叶存在一个呈拓扑状梯度分布的语言功能网络，且该梯度分布与人类语言中语音、语法和语义的功能区分正好基本对应。

在第三章中，我们使用弥散张量成像技术（DTI）考察了第二语言（二语）学习成绩与大脑语言网络结构联结的重组的关系。我们发现，被试刚开始学习二语时，随着成绩的提高，大脑BA6-颞叶通路（弓状束的一部分）的结构联结强度逐渐由左侧化变为右侧化。但是当被试的二语学习成绩达到一定水平后，这一语言通路的结构联结强度又重新回归左侧化。该结果表明（至少一部分）大脑语言网络的结构联结强度可能会随着语言学习而产生快速的动态变化。

在第四章中，我们考察了成人语言能力与其大脑语言通路的结构联结强度之间的关系。我们使用《LLAMA语言能力量表》(Meara, 2005) 测试了语言能力的四种成分：词汇学习、语音辨别、语音-符号对应、语法参悟。结果发现几乎所有这些语言能力都与一个或多个大脑语言通路的结构联结强度显著相关。

在第五章中，我们使用图论技术（graph theoretical techniques）研究了大脑语言网络的复杂结构。我们发现经典的布洛卡氏区和韦尼克氏区在大脑网络中都扮演着结构枢纽的角色。我们进一步考察了与语言相关的CNTNAP2 基因类型对布洛卡氏区和韦尼克氏区作为结构枢纽的特征的影响。 结果发现韦尼克

氏区的图论拓扑结构受到该基因的显著影响。

总而言之，本论文通过使用先进的脑成像技术，于“离线”状态（即没有外显的语言活动）下研究了大脑的语言功能。本研究结果为人们了解大脑语言网络的功能和结构组织提供了有用的信息。本研究结果与前人任务状态下（有外显的语言活动）研究结果之间的一致性表明：即使在没有外显的语言活动进行时，人脑也是一个针对语言功能优化了的、“准备好了”的系统。值得注意的是，本论文也发现某些大脑语言通路的结构联结的偏侧化可能会因受到短期语言学习活动的影响而产生快速的动态变化。这表明在大脑结构网络与外界环境之间有着动态的交互作用。总结来说，一个“准备好了”的大脑语言网络可能是由生理遗传和环境交互两方面的因素共同作用而形成的。

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Curriculum Vitae

Huadong Xiang was born on October 14th, 1978 in Yichang, Hubei, China. After his secondary education, he studied biology at Hubei University in China. He received his bachelor's degree in 2001. After that he worked in the Institute of Psychology, Chinese Academy of Sciences in Beijing as a research assistant. Then he started a master program in psychology at Tianjin Normal University in China in 2002. He received his first master degree in psychology in 2005. After that he worked as a researcher at Shantou University in Canton. In 2006, he was recruited with full scholarship by the Joint European Master Programme in Clinical Linguistics and studied in Milan (Italy), Groningen (the Netherlands) and Potsdam (Germany). He received his second master degree in clinical linguistics in 2007. In December 2007, he started to study at the Donders Institute for Brain, Cognition and Behaviour at Radboud University Nijmegen in the Netherlands as a PhD student. Under the supervision of Prof. P. Hagoort and Prof. D. G. Norris, he mainly investigated the functional and structural organization of the brain networks, and their connectivity pattern and relation to language learning, capacity and language-related genetics. The results of his work have been reported in his thesis.

Besides his scientific career, he founded the “I love brain science” website (52brian.com, in Chinese) which has become the most influential professional-website in Chinese brain researchers. In 2011, he founded the “66nao” start-up business team aiming to apply the advanced brain science to real life. His team won the prize of the competition of overseas start-ups organized by the Chinese Ministry of Education and Ministry of Science and Technology. His team was then invited to China and is going to start a company in the science park at Peking University in Beijing.

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